SAFETY AND EFFICACY OF HYPOTONIC RIBOFLAVIN ASSISTED CORNEAL COLLAGEN CROSSLINKING IN KERATOCONUS PATIENTS WITH THIN CORNEAS (<400MICRONS)

DESSERTATION SUBMITTED FOR

MS (BRANCH III)OPHTHALMOLOGY

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2016

CERTIFICATE

This is to certify that the thesis entitled "**SAFETY AND EFFICACY OF HYPOTONIC RIBOFLAVIN ASSISTED CORNEAL COLLAGEN CROSSLINKING IN KERATOCONUS PATIENTS WITH THIN CORNEAS (<400MICRONS)**" is the original work of **Dr.T.Ajeetha** andwas conducted under our direct supervision and guidance at Aravind Eye Hospitals and Post Graduate Institute of Ophthalmology.

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DECLARATION

I, **DR.Dr.T.AJEETHA** solemnly declare that the dissertation titled "**SAFETY AND EFFICACY OF HYPOTONIC RIBOFLAVIN ASSISTED CORNEAL COLLAGEN CROSSLINKING IN KERATOCONUS PATIENTS WITH THIN CORNEAS (<400MICRONS)** has been prepared by me. I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, diploma to any other university board either in India or abroad.

This dissertation is submitted to the **Tamil Nadu Dr.M.G.R Medical University**, Chennai in partial fulfillment of the rules and regulation for the award of **M.S. Ophthalmology (Branch III)** to be held in April 2016.

Place : Madurai

Date : **Dr.T.Ajeetha**

ACKNOWLEDGEMENT

I take this opportunity to pay my respect and homage to our founder **Dr.G.Venkataswamy**, whose earning desire to achieve his mission "to eradicate needlees blindness" and whose dynamism had led Aravind against all the obstacles to its epitope.

It is aproud privilege and pleasure to express my sincere thanks towards my revered mentor and guide **Dr.Manoranjan Das**, Consultant, Cornea Services, Aravind Eye Hospital Madurai for being a constant source of motivation and encouragement which helped me to structure my thesis.

I offer my sincere gratitude to **Dr.N.Venkatesh Prajna**, Director of Academics, Aravind Eye Care System for his constant support and excellent Guidance throughout my residency programme.

I offer my sincere thanks to **Dr.R.D.Ravindran,** Chairman of Aravind Eye care System for having created an environment enriched with knowledge with all the facilities needed to inculcate wisdom in us .I am privileged to have on my side **Dr.P.Namperumalswamy,** Chairman Emeritus ,Director of Research, **Dr.G.Natchiar,** Director Emeritus (Human Resource Department), **Dr.M.Srinivasan**, Director Emeritus and other Scholars of Ophthalmology, Aravind Eye Care System.

I offer my sincere thanks to **Dr.AshishKumar**, Cornea Fellow, for his constant support and guidance and all the paramedical staff of the Cornea Department for their constant help and excellent cooperation during the study. I also extend my thanks to the Biostatistician, Mr.Vijayakumar and all the faculties of the library who rendered their help during the study.

I sincerely thank my patients without whom this study would not have been possible.

Last but not the least, I would like to thank my parents, my husband, my daughter and all my family members for all their sacrifices and unfailing love towards me.

Finally I would like to conclude with this inspirational quote from our founder Dr.G.Venkataswamy, "Intelligence and capability are not enough. There must also be the joy of doing something beautiful. Being of service to God and humanity means going well beyond the sophistication of the best technology, to the humble demonstration of courtesy and compassion to each patient".

Dr.T.Ajeetha

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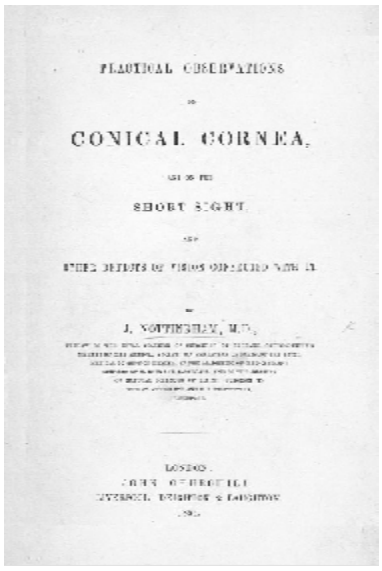
PART I

PART II

INTRODUCTION

History of keratoconus goes back to nearly 3 centuries. In the 18th and 19th century, the earliest description of keratoconus was by Benedict Duddell whose name is still remembered for his discovery of the dudell's membrane or our present day, descemet's membrane of the cornea. Early references and comprehensive understanding of conical corneas was by John Nottingham in his renowed published treatise in1854.[1] Dr.Joannes Taylor gave the first accurate description of keratoconus. Mauchart in 1748 gave the earliest description of keratoconus and described it as "Staphyloma Diaphanum".


PRACTICAL OBSERVATIONS

ON

CONICAL CORNEA,

AND ON THE

SHORT SIGHT,

AND

OTHER DEFECTS OF VISION HITHERTO UNKNOWN OR ILL

BY

J. NOTTINGHAM, M.D.,

LONDON:

JOHN CHURCHILL

PRINCES STREET, SOHO


JOANNES TAYLOR, MEDICUS,

The term keratoconus is obtained from the Greek word "*kerato",* horn, meaning Cornea and "*konus",* meaning Cone.

Keratoconus manifests as a bilateral non inflammatory progressive corneal disorder with characteristic thinning and corresponding steepening of the cornea. This change in corneal morphology brings about alterations in the refractive power, in the form of irregular myopic astigmatism leading to poor vision. It is usually asymmetric in its presentation. It may take many years for the condition to become apparent in the other eye after the initial diagnosis of disease in one eye.

"Forme fruste keratoconus" - This term refers to the other eye of the person which is less affected and which display no clinical findings except for some specific topographic changes.

"Keratoconus suspect"- The eyes with suspicious topography, where the other eye of the person does not have keratoconus.[2]

The ultimate cause which lies behind the development of keratoconus has not yet been understood. However, it appears to be a diverse condition that may be caused by a wide range of unrelated errors in metabolism.

Epidemiology:

Incidence of keratoconus is approximately 50-230 per 100,000 or 1 in 2000 in the general population. Prevalence rate being 54.5/100,000 [Smollin and Thoft].[3]

Age of onset:

The onset of keratoconus classically begins at an adolescent age and progresses until third to fourth decade following which it usually stops its progression. It commonly occurs in isolation.

Sex:

Though keratoconus occurs in all age groups with no sex predilection, a fewer reports showed a higher incidence among females.

Genetics:

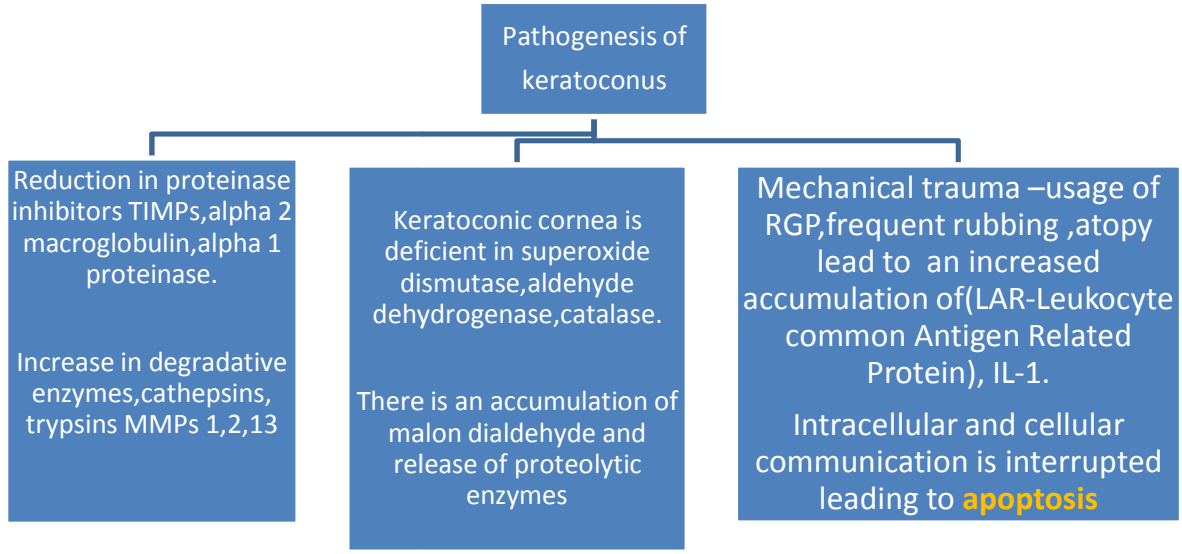
Keratoconus presents as a sporadic disorder, in which only a certain cluster of patients elicit a positive family history with autosomal dominant or autosomal recessive transmission. Cases within the families and the presence of high accordance in monozygotic twins brings about the suspicion of genetics behind keratoconus. Mutations of any genes has not been reported in the multiple loci mapped in familial keratoconus. The assembly of loci implicated in keratoconus suggests that apart from Mendelian mode of inheritance other mechanisms of inheritance is also present. The first degree relatives ,siblings and off springs are the most affected.[4]

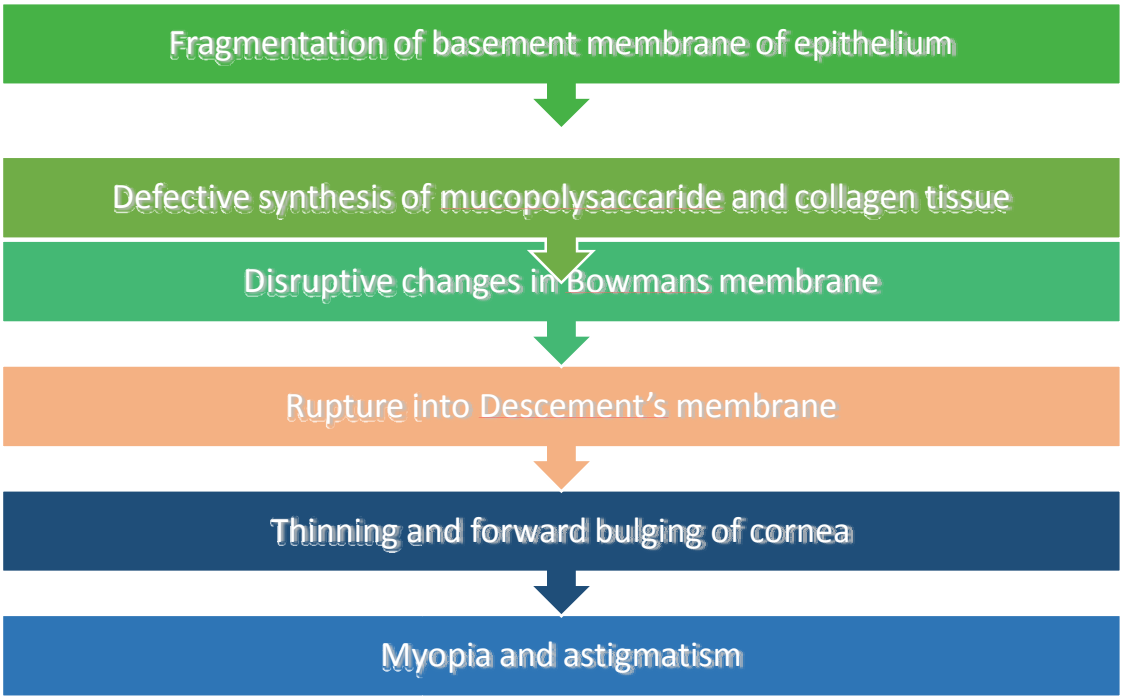
Heterogenous: Multiple genes are involved. Genetic factors with environmental factors play a role in the evolution of keratoconus.

Loci for isolated keratoconus is : 16q22.3-q23,20q12,21p.

Loci for keratoconus associated with other disorder is : 20p11-q11[VSX1 Homoeobox] 17p13(LCA4),17pLCA AIPL-gene.

PATHOGENESIS[5]





Risk Factors:

- Genetic predisposition
- Over exposure of ultraviolet rays
- Often excessive eye rubbing
- Poor fit of contact lens

Systemic Associations:

- Down's syndrome
- Turner's syndrome
- Marfan's syndrome
- Leber's congenital amaurosis
- Atopic keratoconjunctivitis
- Connective tissue disorders
- Disorders of collagen metabolism

CLINICAL FEATURES OF KERATOCONUS

1.History from the patients :

- Frequent change of glasses • Double vision • Polyopia • Strain while reading • Asthenopia • Diminution of vision.

2.Refraction signs:

• Retinoscopy – Scissor's reflex • Progressive Myopia • Increase in irregular astigmatism.

3.Unaided eye examination and Retinoscopy Shows:

Scissoring reflex • Munsen's sign

4.Keratometry Signs:

• Mal-alignment of mires • Mal-apposition of mires • Irregularity of mires• Pulsating mires • Lack of Parallellism • Distorted mires.

5.Videokeratoscopic Signs:

• Compression of mires in affected region • Increased power in isolated area of cone depicted by the colour map

6.Ophthalmoscopic signs:

- Oil droplet reflex

7.Slit lamp Biomicroscopy:

- Steepening •Thinning • Vogt's Striae • Prominent corneal Nerves • Fleischer's ring •Acute Hydrops • Various levels of scarring

8.Progressive status noted by :

- Increase in thinning • Increase in scarring • Increase in curvature • Increase in diameter of the cone

9.Differential Diagnosis:

- Keratoglobus • Terrian's degeneration • Pellucid Marginal degeneration

The morphological signs of keratoconus include :

Early signs:

- Irregular oblique astigmatism
- Retinoscopy showing **"scissoring " reflex**

Keratometry:

Keratometry shows irregular myopic astigmatism where the principle meridians are not perpendicular to one another or in other words are not 90 degrees to one another and there is no superimposition of mires.

Direct ophthalmoscopy:

Reveals an "**oil droplet**" reflex

Rizzuti's sign –Light shown from the temporal side will be displaced beyond the nasal limbus in the presence of very high astigmatism and steep curvatures.

Anterior Segment Examination With Slit Lamp shows :

Vogts striae -Fine vertical deep stromal striae

Prominent corneal nerves

Fleischer's ring—

Fleischer's ring is a pigmented brown ring which occurs due to the accumulation of ferritin within the corneal basal epithelium .

There are associated breaks in the Bowman's membrane, and accumulation of Periodic Acidic Schiff -positive material. There is associated thinning of stroma and altered corneal keratocyte and endothelial morphology. [6]

Biochemical and Histopathological examination shows that corneas with keratoconus have :

- Lowered Tissue Inhibitors of Metalloproteinases(TIMPs),
- Enhanced collagen breakdown,
- IL-4 receptors – Overexpression,
- Apoptosis of the stromal keratocytes,
- Variations in the distribution and orientation of collagen,
- Raised levels of catabolic enzymes.

Late signs

i. Progressive corneal thinning associated with high irregular myopic astigmatism.

ii. Steep keratometry readings .

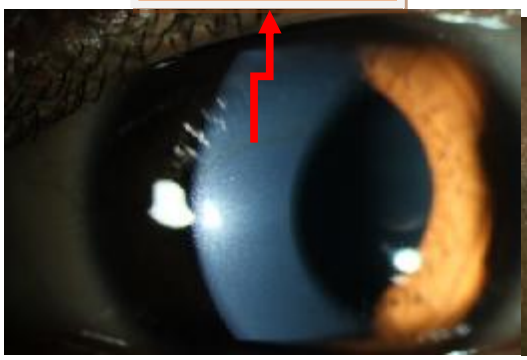
iii. Thinnest apex of the cone is displaced inferiorly.

iv. Protrusion of the cornea causing bulging of the lower lid –Munson's sign.

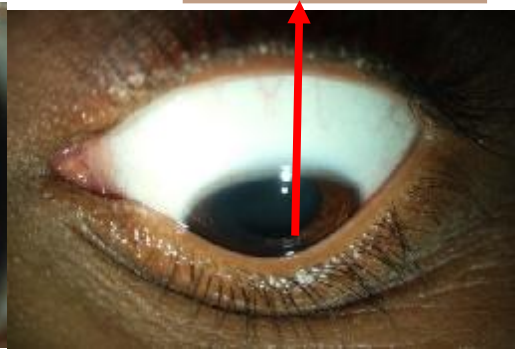
v. Stromal scarring in advanced cases following acute hydrops.[7]

Keratoconus

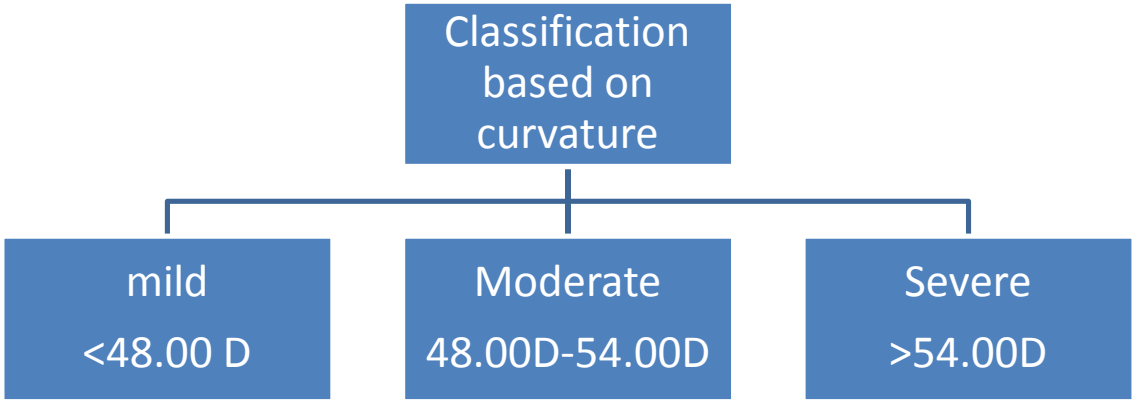
Fleischer's

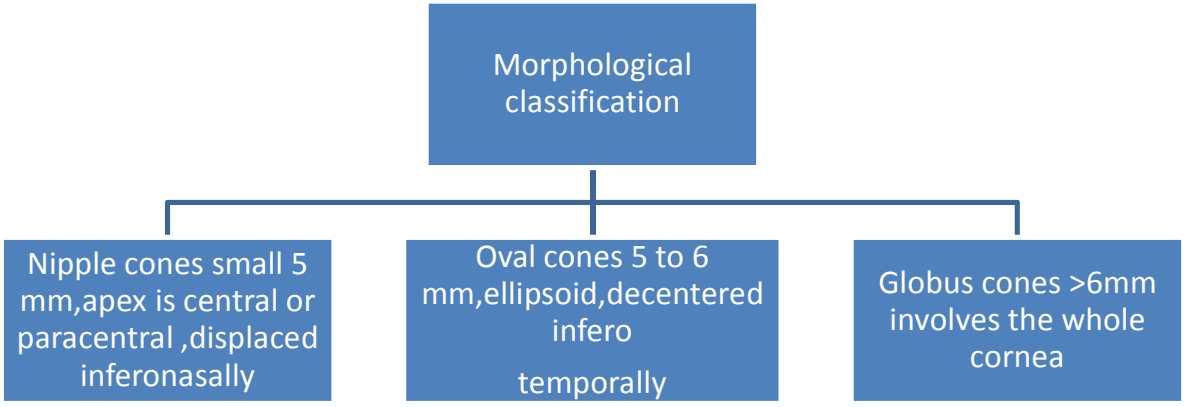


Munsen's Sign



CLASSIFICATION





"<u>Modified Amslers Krumeich classification</u> "

Based on

i.Mean K reading

ii.Anterior curvature sagittal map

iii.Thickness at the thinnest location

iv.Refractive error of the patient

Stage 1 • Mean K Reading at the centre<48 D • Myopia,induced astigmatism or both <5.00 D • Eccentric steepening • Vogt's striae,no scars
Stage 2 • Mean K reading at the centre<53.00D • Myopia with astigmatism of 5 .00D to 8.00D • No scar • Thickness of cornea > 400 microns
Stage 3 • MeanK reading at the centre>53.00 D • Myopia ,induced astigmatism of 8.00 D to 10.00D • No evidence corneal scarring • Thickness of cornea between 200 to 400 microns
Stage 4 • Mean Kreading at the centre>55.00 D • Refraction impossible • Presence of central corneal scar • Thickness of cornea < 200 microns

MANAGEMENT OF KERATOCONUS

Optical correction:

Spectacles:

Indicated in early keratoconus to correct astigmatism.

Contact Lenses :

In the early phases of the disease process, soft toric lenses may suffice. However in advanced disease, rigid gas permeable lenses, including multicurve spherical based lenses, aspheric lenses, hybrid lenses with a rigid central portion with a soft hydrophilic spherical skirt and bispheric lenses may be required. They do not arrest the progression but only improve the vision. These lenses are difficult to fit in irregular corneas and the fitting would require a great deal of time and expertise. Their fitting becomes even more difficult as the disease advances especially due to the formation of nodular scars at or near the apex of the cone.

Common Complications from Contact Lens Use:

i. Corneal abrasions

ii. Apical scarring

iii. Vascularisation from contact lens induced hypoxia

iv. Lens discomfort

Hybrid Contact Lens

REFRACTIVE SURGERY FOR KERATOCONUS:

Keratoconus or forme fruste keratoconus was considered to be an absolute contraindication to refractive surgery because of postoperative keratectasia in susceptible corneas. It has been reported that there has been an increase in keratectasia, myopic astigmatism after laser due to progressive corneal steepening which occurs as early as 1 week or several years later after the surgery. The incidence is said to be more after Laser Assisted *In Situ* Keratomileusis but it can also occur following Photo Refractive keratectomy (PRK). The topographic changes and clinical features of keratectasia are very similar to that of keratoconus**.**

Risk factors associated with keractectasia

- Thinner preoperative corneas
- Presence of High myopia

- Thinned residual stromal beds
- Preoperative topography suggestive of keratoconus or forme fruste keratoconus in either of the eyes
- A strong family history suggestive of presence of keratoconus.

The cause of keratectasia, post refractive surgery is not clear but it is thought that it occurs due to laser induced stress which further triggers alterations in the biomechanical properties of the corneas which are susceptible. The electron microscopic studies of keratectatic corneas showed ruptures in the Bowman's layer, typical of keratoconus as found in post-excimer laser keratectasia.

keratectatic and keratoconic corneas

- Showed thinned out collagen fibrils
- Decreased interfibril distance
- immunohistochemical analysis shows differences in protease inhibitor 1 and transcription factor Sp1, which shows that the pathological changes of the two conditions differs.

PHOTOREFRACTIVE KERATECTOMY :

Photorefractive Keratectomy is preferred over LASIK and is considered to be a safer option for keratoconus suspects and those with thin corneas because it has an advantage of leaving behind an adequate residual stromal bed after surgery than LASIK and has usually been considered to be a safer option in keratoconus suspects. There was no evidence of sudden progression of the disease or development of keratoconus. Based on this inference it has been concluded that Photorefractive Keratectomy appears to be safe in keratoconus suspects with stable refraction but observation might differ in eyes with early frank keratoconus.

Excimer laser Photo Therapeutic Keratectomy has been useful in the management of keratoconus corneas with nodular scars which causes contact lens intolerance. It even delays the need of penetrating keratoplasty in patients with advanced disease.

INTRASTROMAL CORNEAL IMPLANTS:[8]

Intrastromal corneal rings are of a potential benefit for the contact lens intolerant keratoconus patients with clear visual axis. It delays the need of corneal transplantation. Intrastromal corneal rings such as Intacs and Ferrara rings are segments made of polymethyl methacrylate and acrylic polymers

are used in the treatment of mild to moderate keratoconus to improve contact lens tolerance.

Pre-requisites of Intacs :

i. Keratoconus should be non-progressive

ii. Absent central corneal scarring

iii. A minimum pachymetry at the site of implantation should be 450 microns

The two polymethylmethacrylate (PMMA) arcuate rings are inserted into the corneal midstroma through the channels created either with a mechanical keratome or with a femtosecond laser to achieve central flattening of the surface. The amount of flattening produced and the reduction in the amount of myopia makes the patients tolerant to contact lenses. It brings about modifications in the refraction by changing the shape of the cornea. It is currently approved only for the management of myopia. But has been used as an off label use in the management of keratoconus.

Complications:

1. The technique of manual tunnel creation with a keratome can cause epithelial defects at the keratotomy site

2. Perforations
3. Uneven placement of the segments
4. Epithelial cells migration into the channel
5. Stromal thinning
6. Infection.

KERATOPLASTY:

Penetrating keratoplasty procedure has got 90% success rate in keratoconus and 10% and 20% of keratoconus patients will require a keratoplasty, and is considered to be the definitive indication in the more advanced stages.

The indications for keratoplasty in keratoconus:[9]

i. Progressive corneal thinning

ii. Presence of central corneal opacities

Patients with advanced keratoconus may sometimes present with sudden onset of painful decrease in vision. On anterior segment examination by slit lamp biomicroscopy, the conjunctiva shows diffuse congestion with diffuse stromal opacity in the cornea. This condition is termed as “Acute Hydrops”.

Pathogenesis of Acute Hydrops :

It is caused by the breaks in the descemets membrane with absorption of aqueous in the stroma through these breaks with eventual resolution of edema after a few weeks or months which is ultimately replaced by a scar. Acute hydrops is not an indication for penetrating keratoplasty as the scars following acute hydrops are usually paracentral. The flattening of the cornea induced by scarring makes the keatoconus patients more tolerant to contact lenses.

Treatment of Acute Hydrops :

i. Cycloplegics
ii. Steroids or Nonsteroidal anti-inflammatory medications
iii. 5%Hypertonic saline Or iv.Bandage contact lenses

Limitations and complications of Penetrating keratoplasty:

i. Suture technique and size of the graft
ii. Disease recurrence in the recipient stroma due to progressive thinning
iii. Vascularised graft
iv. There might be a high degree of graft astigmatism .
v. The corneal nerves are severed leading to reduced corneal sensitivity
vi. Poor graft survival due to the continuous loss of endothelial cells of the donor.

DEEP ANTERIOR LAMELLAR KERATOPLASTY:

One of the newer surgical options for keratoconus is, Deep Anterior Lamellar Keratoplasty (DALK), involving exchange of only the epithelium and stroma. This approach has the advantage of preserving the endothelium of the recipient cornea, thus reducing risk of infection and rejection. The DALK technique involves manual dissection or dissection using "Big Bubble Technique of Anwar" which often gives an uneven bed and an irregular interface with a satisfactory visual outcome. With the improvements in surgical technique and advances in instrumentation which has helped to match between patient and donor corneas, the visual outcomes were similar to those of Penetrating keratoplasty.

CORNEAL COLLAGEN CROSS LINKING(CXL)

Collagen cross-linking using UVA light and riboflavin (vitamin B2) mainly targets stromal stability. It is the only procedure devised to arrest the progression of the disease.The idea of using CXL for corneal stiffening was first formulated in Germany in the 1990s by Prof Theo Sieler, Prof Wollensak and Prof Eberhard Spoerl at the University of Dresden, Germany.[10]

BACKGROUND

What is Crosslinking ?

Crosslinking is the creation of bonds that connect one polymer chain to another. The bonds can be covalent or ionic.

What is a polymer?

A polymer is defined as a chain of monomeric material - either a synthetic polymer or a protein. Crosslinking of polymers changes their physical properties. For instance rubber molecule when cross linked will cause a decrease in its flexibility and an increase in its rigidity.

Early Applications Of Crosslinking:

Crosslinking has its application in bioengineering and dentistry. This phenomena of creation of crosslinks between the polymer molecules to improve the mechanical strength of materials has been used in the manufacture of plastics and the production of prosthetic heart valve.

Early Application of Crosslinking in human eye

Hettlich et al in 1992 devised a method to perform lens implantation following phacoemulsification.They devised a method which included the injection of a monomer into the lens capsule, followed by intracapsular polymerization of the material by exposure to light (400-500 nm). They found that the substance did not significantly damage the surrounding ocular tissues. This method was one of the early examples for the use of light energy to induce intraocular structural changes.

Corneal collagen becomes progressively cross-linked with age, and this can be regarded as a natural physiological ageing process. Increased crosslinking is associated with increasing rigidity, and this explains why the progressive ectasia seen in keratoconus occurs primarily in younger patients. Diabetic patients seem to be protected against progressive keratoconus, and this may be related to increased collagen cross-linking associated with hyperglycaemia, the so called 'Maillard reaction'.

Spoerl, Huhle and Seiler in 1998 were the first to introduce the common technique which involves involves the use of riboflavin (vitamin B2), which is exposed to ultraviolet A light (UVA) radiation (370nm), which is considered to be safe for the ocular tissues ,delivered at the rate of 3 mW/cm2 (5.4 J/cm2).

Riboflavin:

Riboflavin molecule has a molecular weight of 376.37 g/mol and it is hydrophilic in nature.

The Two Roles of Riboflavin in Crosslinking :

i. Its role as a photosensitiser

ii. Its role in the limitation of the ultraviolet radiation to the desired treatment depth.

During photosensitization, free radicals produced will induce a reaction resulting in the formation of covalent bonds between the collagen microfibrils.

Riboflavin Molecule and UVA Light:

The normal spectrum of light includes Ultraviolet C (220 to 290 nm), Ultraviolet B (290 to 320 nm), and Ultraviolet A (320 to 340 nm), infrared radiation, and visible light of which UVC is blocked by the ozone layer. Where as UVA and UVB penetrate to the surface of the earth and are known to cause damage to ribonucleic acids. UVA spectrum has the potential to cause corneal endothelial cytotoxicity. The typical UVA surface dose which is clinically used for CXL is only 5.4 J/cm^2.

Though riboflavin and UVA application is considered to be a safe and well tolerated procedure, complications can occur. Endothelial cytotoxicity is always a concern with any corneal surgery. Animal studies showed when a

cornea less than 400 microns thick is irradiated with a standard dose of 5.4 J/cm^2 (3 mW/cm^2), the endothelial dose can reach cytotoxic levels and cause significant necrosis and apoptosis of endothelial cells within 24 hours of application. Utmost caution should be exercised in these patients. In such patients application of hypotonic riboflavin causes corneal swelling to levels above 400 microns or a reduction of UVA dose has been used. One study showed that reducing the standard dose of UVA to 2mW/cm^2 produced a significant mechanical stiffening effect and an increase in resistance to enzymatic digestion. With this low irradiance level the endothelial UVA dose is only 0.54 J/cm^2 (0.3 mW/cm^2), well below the threshold level of endothelial cytotoxicity.

EFFECTS OF CROSS-LINKING ON THE CORNEA:

In Vivo Confocal Microscopy,[11] a prospective cross sectional study conducted by Engin Bilge Ozgurhan et al in 2013 to analyse the corneal microstructure in patients with manifest keratoconus, subclinical keratoconus and the relatives of patients with keratoconus who were topographically normal and in healthy controls with respect to mean basal epithelial density, endothelial cell density and the sub-basal nerve fibre diameter concluded that confocal microscopy may be useful in the determination of early corneal microstructural

changes before the manifestation of typical or subtle topographic signs of keratoconus .

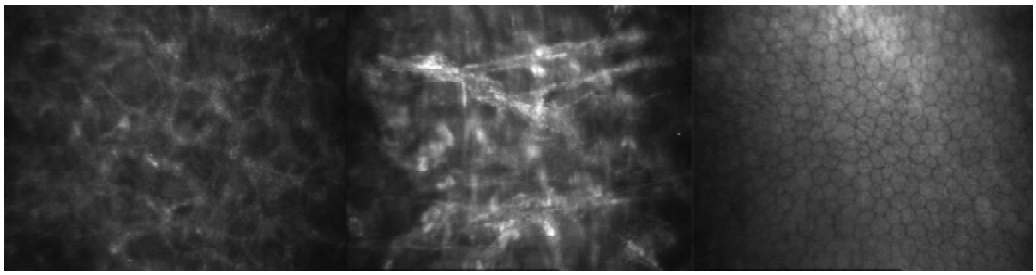
In the prospective study of Charlotte Jordan et al in 2014 in their analyses of corneal microstructural changes has demonstrated early apoptosis of the keratocytes in the eyes that have underwent collagen cross linking. Confocal microscopy has demonstrated loss of the subepithelial nerve plexus and midstromal nerve fibres with stromal edema. Keratocyte repopulation is seen after 3 to 12 months of treatment along with nerve plexus regeneration.

The postoperative subepithelial haze is due to the keratocyte repopulation and due to the increased reflectivity of the extracellular matrix seen. The hyper refractile stuctures formed a clear demarcation line between the anterior treated zone and the posterior untreated stromal zone. But deep posterior stroma behind the treatment zone and the adjacent corneal epithelium remained normal during the entire study period.

In the studies of in vivo and ex vivo confocal microscopy showed a apoptosis of all the keratocytes and honeycomb like stromal edema in the anterior approximately 320microns (range being 270-350 microns)in the early postoperative period in corneas treated after collagen crosslinking.

Confocal Microscopy :

1 2 3



(1) Stroma showing loss of keratocytes with anterior stromal edema

(2) Mid to posterior stroma showing striate reflections

(3) Healthy endothelium three months after crosslinking.

The major drawback of collagen crosslinking is its effect limitation to anterior 300 to 350 microns of the corneal thickness which has been confirmed on confocal microscopy examination. The factor behind this is that riboflavin decreases UVA penetration across the stroma. A stromal demarcation line may be seen in two weeks after treatment, which gradually fades after three months. In a study by Wollensak, Spoerl and Seiler to study the effect of CXL in rabbit corneas showed that the cytotoxic dose of UVA reached the level of the endothelial cells at an irradiance of $3mW/cm^2$ if the corneal thickness was less than 400 micron.

The criteria proposed for a‘safe’ treatment:

i. Removal of the epithelium to allow riboflavin absorption.

ii. 0.1% riboflavin should be applied for half an hour prior to UVA.

iii. UVA irradiance should be delivered at at the rate of 3 mW/cm^2

iv. The minimum stromal thickness should be maintained at 400 microns or more.

TREATMENT PROTOCOLS :

The most widely used treatment protocol is based on the "Dresdens Protocol".

PHOTO REFRACTIVE KERATECTOMY AND CXL:

Photo Refractive Keratectomy combined with corneal collagen cross-linking indicated for progressive keratoconus. The collagen crosslinking can either be done at the same time as the PRK or in separate sittings. The procedure used is to use minimal ablation, making sure that the residual corneal thickness postoperatively is not less than 400 microns. Refractive and visual results, as has been very good, though the limited ablation often results in only partial correction of refractive error. Simultaneous PRK/collagen cross linking, rather than treatments at separate sittings may lead to a better penetration of the riboflavin solution through the ablated stroma. If performed some time after the collagen cross-linking procedure, some of the stiffened crosslinked anterior cornea is removed thereby reduces the benefit of collagen crosslinking.

INTACS AND CORNEAL COLLAGEN CROSSLINKING:

Intacs have an additive effect when combined with collagen crosslinking induces increased biomechanical rigidity in the cornea which may inturn lead to increased rigidity locally or across the Intacs segment, producing further flattening.

CORNEAL CROSS LINKING IN CORNEAL NON ECTATIC DISORDERS:

Bullous Keratopathy and Other Causes of Corneal Edema:

Bullous keratopathy caused by the failure of the endothelial pump mechanism which causes fluid accumulation in the extracellular space between the stromal lamellae. Corneal collagen crosslinking increases the cornea's resistance to swelling and has been evaluated for the treatment of pseudophakic bullous keratopathy and other causes of corneal edema. Edematous corneas when treated treated with CXL demonstrated increased collagen fibril linkages and bonding in the anterior stroma when compared with untreated controls. However this effect was less witnessed in corneas with advanced fibrosis with edema. The effect of the procedure was short lasting and appeared to wear off after 3 months of the procedure. The use of corneal collagen crossslinking led to thinning of cornea and a marked improvement in

visual acuity. There was marked improvementin corneal thickness, pain and corneal haze following corneal collagen cross linking.

FOR REFRACTORY INFECTIOUS/ULCERATIVE KERATITIS:

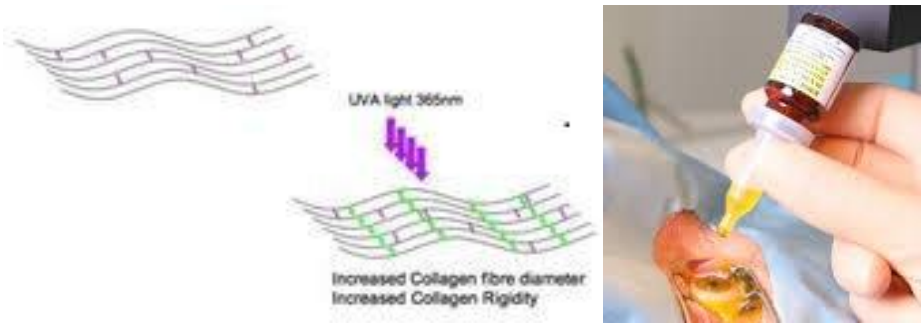
Crosslinking was considered as an adjuvant in the treatment of keratitis and in all cases, progression was arrested after treatment with CXL thus preventing the need for keratoplasty. This important use of CXL should not be underestimated, as emergency penetrating keratoplasty carries the risk of reinfection as 15% and rejection high as 38%.[12] However standard keratoplasty these rates are less than 10%. Crosslinking also carries the benefit of not increasing the antibiotic resistance, making it especially beneficial for cases refractory tostandard therapy or in conditions where resistance is strongly suspected.

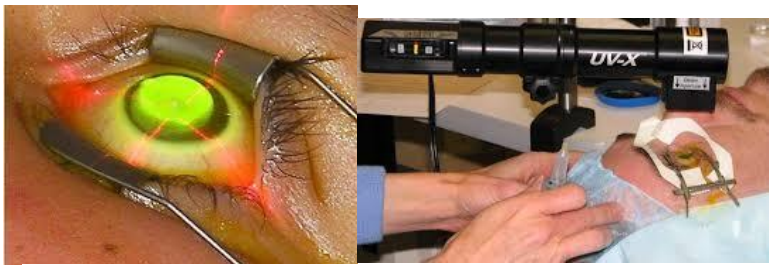
OTHER NOVEL APPLICATIONS OF CXL:

CXL has been currently being studied in a number of other settings, in ocular tissues apart from the cornea. For example, Wollensak et al [13] showed enhanced scleral collagen crosslinking in rabbits which increased the mechanical strength of sclera, which shows that this may be one of the options in the management of progressive axial myopia. But it should not exceed the retinal cytotoxic dose. Thornton et al[14] proved in his study that stiffening peripapillary sclera in pigs reduces the biomechanical susceptibility of the optic

nerve / laminacribrosa complex to intraocular pressure elevation, which could be a beneficial future treatment for low tension glaucoma.

CXL PROCEDURE





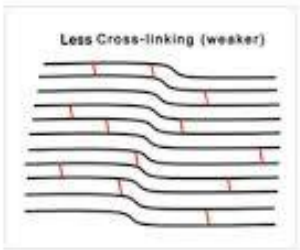


Figure 1: Corneal layers BEFORE CXL

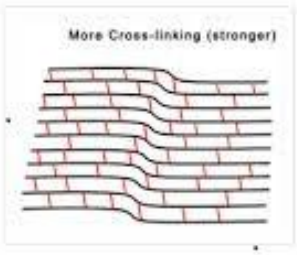


Figure 2: Increased cross-linking AFTER CXL

HYPOTONIC CORNEAL COLLAGEN CROSS LINKING:

The current corneal collagen crosslinking treatment protocols induce crosslinks confined to the anterior 250–350 mm of the corneal stroma. So in order to protect the endothelium, CXL inclusion criteria requires a minimal corneal thickness of 400 µm after removal of the epithelium.[15] In many cases of advanced progressive keratectasia, however, minimal stromal thickness is below 400 µm and represents the only parameter preventing safe CXL.

This is overcome by a modified technique of applying hypoosmolar riboflavin solution which induces stromal swelling before UVA irradiation. The thinnest cornea with a minimal thickness of 320 microns after removal of the epithelium is a prerequisite and a swelling of at least 80 additional microns is needed to achieve the minimal corneal thickness of 400 µm for a safe corneal collagen cross linking procedure.

Different Riboflavin solutions available :

Standard riboflavin solution with dextran for epithelium-off procedure :

- Riboflavin solution with dextran
- The instillation time is 20 minutes
- Ingredients: 0.1 % riboflavin (Vitamin B2) with 20 % dextran 500

Standard riboflavin solution without dextran for epithelium-off procedure:

- Does not decrease the corneal thickness
- Instillation time: 20 minutes
- Ingredients are 0.1 % riboflavin (Vitamin B2), 1.1 % HPMC

Trans epithelial solution for epi-on procedure :

- Instillation time: 20 minutes
- Pre-loaded syringe containing 2.0 ml liquid
- The ingredients are 0.25 % riboflavin (Vitamin B2), 1.2 % HPMC, 0.01 % benzalkonium chloride(BAC)

Hypotonic Riboflavin Solution for corneal swelling

- To induce osmotic swelling of thin corneas (< 400 μ)
- Instillation time is one drop every five seconds until corneal thickness has reached 400 μ .
- Ingredients are 0.1 % riboflavin (Vitamin B2)

Riboflavin Solution for use with LASIK procedures on thin corneas

- Recommended usage after flap preparation and excimer treatment.
- Apply three to five drops on stroma, replace the flap wait 3 – 4 minutes and then open the flap.
- Rinse off riboflavin and replace the flap and irradiate with half of the recommended energy (1/2 of the time).

- Ingredients: 0.23 % riboflavin (Vitamin B2).

FACTORS CONTROLLING CORNEAL HYDRATION :

Corneal hydration is based on certain crucial factors such as active transendothelial transport, epithelial and endothelial barrier. If any one of these mechanisms is impaired edema occurs.

The corneal stroma shows a swelling pressure of 50 to 60 mm Hg at normal physiological situations. Swelling of the corneal stroma can be obtained by using a solution with a low colloidal osmotic pressure such as hypoosmolar solution. The deepithelized cornea can swell to two times its normal thickness when irrigated with a hypoosmolar solution. This phenomenon is not due to an increase in the diameter of the collagen fibrils but rather due to the hydrophilic nature of the stromal proteoglycans. This property is used to increase corneal thickness before the corneal collagen crosslinking procedure.[16]

Holopianen and Krootila[17] in their study used distilled water repeatedly during the procedure to swell the corneal stroma without compromising on the efficacy and safety and also by lowering the stromal riboflavin concentration.

REVIEW OF LITERATURE

ANIMAL STUDIES :

Wollensak et al[18] introduced the procedure of collagen cross linking in 2003.They evaluated the effect of corneal collage cross linking treatment using human and porcine corneas. The corneas were treated with UVA,(370 nm.irradiance 3 mW/cm²) for half an hour following treatment with riboflavin. The treated corneas were subjected to a static stress test using a biomaterial tester. A significant increase in rigidity was noted. A greater stiffening effect of the human corneas was noted due to its relative thin nature.

Wollensak et al[19] studied the effect on corneal keratocytes for the possible cytotoxic effect of riboflavin and UVA treatment in 2004. The corneas of thirty four New Zealand white rabbits were subjected to corneal collagen cross linking following which the rabbits were euthanized four to twenty four hours postoperatively. The histopathological evaluation of the treated corneas showed apoptosis of the keratocytes .The apoptotic keratocytes were confined to anterior 50 microns of the control eyes. The depth of the apoptotic cells in the treated eyes varied depending on the strength of the irradiance applied. Dose dependent keratocyte damage upto a depth of 300 μm in human corneas can be expected following treatment with UVA dose of 5.47J/cm².

Kohlhaas et al [20] in 2006 studied the depth of corneal tissue upto which the stiffening effect of corneal collagen crosslinking was detectable. 40 enucleated porcine corneas half of which underwent treatment with riboflavin and UVA while the remaining half served as the control. After treatment 2 flaps of 200 microns each were cut using microkeratome. Corneal strips of 7 mm length and 5 mm width were prepared and were subjected to stress strain behaviour using material tester. There was a significant increase in the stiffening of treated anterior corneal flaps and the control group. This greater stiffening effect in the anterior stroma was attributed to the absorption of greater percentage of UVA by the anterior 200 microns of the corneal stroma. Thus crosslinking has no effect on the deeper structures and endothelium.

CLINICAL STUDIES:

Wollensak et al [21] in 2003 were the first to evaluate the clinical effect of corneal collagen crosslinking using riboflavin and UVA for halting the progression of keratoconus. Twenty three eyes of twenty two patients with moderate to advanced progressive keratoconus were subjected to riboflavin drops and UVA irradiation (370nm,3mw/cm²) following corneal epithelial debridement. Postoperative evaluation included testing for vision, slit lamp evaluation, corneal topography, endothelial cell count and clinical picture. All

the eyes in the study failed to progress following treatment. In sixteen eyes regression of keratoconus with a 2.01D reduction in maximum keratometric value and a 1.14D reduction in the refractive error was noted. There was no effect on the intraocular pressure, corneal transparency and endothelial density.

Wollensak et al [22] in 2006 evaluated the progression of keratoconus in 60 eyes subjected to cross linking treatment over a period of 3 to 5 years. The conclusion of the study showed a definite halt in the progression of the disease in all the eyes with a minimal reversal of keratoconus in 31 eyes. An improvement in best corrected visual acuity was also noted.

Seiler et al [23] in 2006 studied the cross linking procedure in 16 patients of keratoconus with a maximum pachymetry of 60D and a central corneal thickness of at least 400µ.The corneal epithelium was mechanically removed and riboflavin drops of 0.1%instilled repeatedly for 20 minutes. Irradiation with UVA light at an irradiance of 3mw/cm² at a working distance of 1 cm were given. The biomicroscopic and topographic evaluation of the eyes were carried out preoperatively and at subsequent followups. A thin demarcation line was observed at around 300µ of corneal depth on the slit lamp examination in 14 of the eyes studied.

Mazotta et al[24] in 2007 evaluated the eyes with advanced keratoconus especially the changes in the corneal stroma following the treatment with

collagen crosslinking. Corneal collagen cross linking procedure was performed in 10 patients with progressive keratoconus and assessed by means of Heidelberg Retinal Tomography II Rodstock Corneal Module in Vivo Confocal microscopy. The eyes that showed progression were treated while the fellow eyes served as the control.

The treated eyes were evaluated at 1, 3, 6 months postoperatively with confocal microscopy. Stromal edema with an increased refraction of the keratocytes were noted in the anterior and intermediate stroma. Resolution of edema with associated keratocyte repopulation was observed after 3 months. Complete keratocyte repopulation with increased stromal density was noted at 6 months. No endothelial cell damage was noted postoperatively.

Santonja et al [25] in 2008 reported a case presenting with multiple corneal infiltrates following an uneventful corneal collagen cross linking procedure in the affected eye. Microbiological evaluation confirmed as staphylococcal epidermidis keratitis. The patient was put on fortified antibiotics. It responded well to the antibiotic treatment and there was a significant increase in visual acuity and decrease in spherical equivalent between preoperative and the postoperative period with minimal residual stromal haze following treatment.

Sharma et al [26] in 2009 reported a female patient presenting on the fourth postoperative day with complaints of redness ,pain and defective vision in her treated eye with corneal collagen cross linking. Microbiological examination from the corneal and contact lens scrappings confirmed the organism to be pseudomonas .The infiltrate responded to treatment with antibiotics but leaving behind a leucomatous corneal opacity.

George D Kymionis et al [27]in 2011 studied 14 eyes out of 21 patients with a corneal thickness of less than 400μ following epithelial debridement. The CXL procedure was performed using the standard protocol. Preoperative and postoperative uncorrected and best corrected visual acuity and corneal topography was performed at 1, 3, 6, 12 months postoperatively. Corneal endothelium was evaluated using confocal scanning laser ophthalmoscope. No intraoperative and postoperative complications were noted. A significant decrease in endothelial cell density was noted.

Adriano Magli et al [28] in 2013 performed a study to compare the safety and efficacy of epithelium off corneal collagen cross linking with transepithelial cross linking in paediatric patients with progressive keratoconus. They noted an improvement in mean K, surface asymmetry index at twelve months post operatively which was the same between the two procedures. Inference of the study was transepithelial CXL seemed to be less painful, with similar

effectiveness and with a fewer complications than epithelium off CXL at twelve month follow up.

Fredrick Raiskup,Eberhard Spoerl [29] in 2011 evaluated the one year results of keratoconic eyes with thin corneas that were treated with hypoosmolar riboflavin solution and ultraviolet A assisted collagen cross-linking (CXL).It was a retrospective, nonrandomized study undertaken at Carl Gustav Carus University Hospital, Dresden, Germany. Thirty-two eyes of 29 patients with progressive keratoconus and a corneal thickness of less than 400 μm (without the epithelium) were subjected to hypotonic riboflavin assisted CXL. Follow up was done before and after the procedure with examinations comprising of evaluation of visual acuity, corneal topography, slit-lamp microscopy, and corneal thickness measurements**.** Results showed the stability of keratoconus, one year after cross-linking. Hypoosmolar riboflavin preserved cross-linked corneas from developing stromal opacities.

Farhad Hafezi et al [16] in 2009, conducted a clinical study in hyposmolar riboflavin assisted CXL technique in 20 patients with progressive keratoconus and iatrogenic keratectasia after refractive laser surgery. It has been noted that the central stromal thickness after abrasion of the epithelium was atleast 320 μm measured by ultrasound pachymetry. The conclusions of the study at 6 months follow up showed no signs of postoperative endothelial damage. Pentacam

Scheimplug imaging showed no progression of K-Mean. However inter individual variation in the intraoperative stromal swelling was observed. Swelling of the deepithelised corneal stroma can be achieved using a solution with a low colloidal osmotic pressure to twice its thickness creating collagen free lakes without increase in diameter of collagen. Thus the intraoperative swelling of the cornea has widened the application of corneal collagen crosslinking in cornea which would otherwise not be suitable for treatment due to decreased stromal thickness.

Farhad Hafezi [30] in 2011 reported a case of failed corneal collagen cross linking for progressive keratoconus after preoperative stromal swelling with hyposmolar riboflavin in extremely thin cornea. Progression was noted at 3 months and 6 months postoperatively. Outcome of this case suggests that a minimal preoperative stromal thickness of 330 microns is needed for a successful CXL procedure. The thoughts from this study is that a for standard technique of collagen cross-linking in keratoconic corneas (> 400 microns) crosslinks were induced in about 300 microns of the anterior stroma which constitutes nearly about 75 % of the corneal thickness . So when a cornea with thickness of only 268 microns as in this study was subjected to CXL, crosslinked 75% of 268 microns (205 microns only) and when it has returned to its normal thickness after swelling such a limited portion of crosslinked cornea

would not be sufficient to arrest an ectatic process. So there should be a minimal preoperative thickness according to the equation Thickness (X) of 250=75% times X. In other words a minimum preoperative thickness of atleast 330 microns should be present.

Charlotte Jordan et al [31] in 2014 in their analyses of corneal microstructural changes has demonstrated, early apoptosis of the keratocytes in the eyes that have underwent collagen cross linking. Confocal microscopy has demonstrated stromal oedema, loss of the subepithelial nerve plexus and midstromal nerve fibres and increased reflectivity in the midstroma. In 3 to 12 months after treatment, keratocyte repopulation is seen, along with regeneration of the nerve plexus.

The post operative subepithelial haze is due to the keratocyte repopulation and due to the increased reflectivity of the extracellular matrix seen. The hyper-reflective structures formed a clear demarcation line between the anterior treated zone and the untreated posterior stromal zone .

Vedat Kaya,Canan Asli et al [32] conducted a study to monitor corneal thickness in corneal ectatic diseases during crosslinking by using isoosmolar riboflavin solution with 20% dextran and hypoosmolar riboflavin solution without dextran. The corneal thickness measurements were obtained at five different times, following epithelial removal, following the application isotonic

riboflavin solution for half an hour, following the application hypotonic riboflavin for 10 minutes, and after ten and thirty minutes of isotonic riboflavin solution application.

- The pachymetric measurements at the thinnest point decreased significantly after the application of isoosmolar riboflavin solution for thirty minutes.
- There was a significant increase after hypoosmolar riboflavin application for ten minutes . This artificial swelling effect was only shortlasting.
- The thinnest pachymetric readings decreased significantly after

10 and 30 minutes of isoosmolar riboflavin application compared with thickness at the end of of applicaton of hypoosmolar riboflavin .

Conclusions:

The iatrogenic swelling effect of the hypoosmolar riboflavin solution might be shortlasting which is overcome by using only hypoosmolar riboflavin for preoperative stromal swelling and during irradiation which may prevent the thinning effect of isosomolar solution.

Mazotta et al[33] were the first to describe stromal opacities following corneal collagen cross linking.

Raiskup Wolf et al[34] indicated that the cases with advanced keratoconus presented with complication of stromal opacities with an incidence rate of 8.6%.

Naomi et al [35] in 2012 described 3 cases with deep stromal opacity that occurred several months after corneal collagen crosslinking. 3 patients, a 36 year old, a 19 year old, a 14 year old underwent CXL procedure based on the Dresdens protocol. After removing the epithelium, hypotonic riboflavin was applied until the stroma swelled and the eyes were then exposed to UVA irradiation. In all the cases epithelium healed without delay with a mild stromal infiltration after the procedure with the inflammation resolving in a week. At one month postop no stromal opacity was present. After a few months a deep inferior paracentral stromal opacity developed which did not affect the visual axis. Postoperative inflammation would have played a crucial role in the pathogenesis.

Aleksandar stojonovic et al [36] in a study to compare safety and efficacy in the treatment of progressive keratoconus with epithelum on and epithelium off CXL with a secondary aim to evaluate the efficacy of CXL when hypotonic 0.5% riboflavin used as a photosensitizer for both the procedure. They observed that the uncorrected and best corrected visual acuity improved significantly in both the groups. Refraction, topography and aberrometry showed nonsignificant

changes. Thus conclusion of the study was both epithelium on and epithelium off CXL using hypotonic 0.5% riboflavin were equally safe and effective in the stabilisation of keratoconus.

LACUNAE IN KNOWLEDGE

There are only a few prospective studies are available which evaluated the safety and efficacy of hypotonic corneal collagen cross linking in thin keratoconic corneas among the South Indian population .This prompted us to undertake this study.

AIM AND OBJECTIVES

To evaluate the safety and efficacy of corneal collagen cross-linking (CXL) treatment with hypotonic riboflavin and ultraviolet-A (UVA) irradiation in patients of progressive keratoconus with thin corneas (<400 microns)

Objectives:

1. To evaluate the effectiveness of hypotonic corneal collagen crosslinking procedure on stabilisation of the progression of Keratoconus with thin corneas(< 400 microns)
2. To find out the safety of hypotonic corneal collagen crosslinking.

Outcome measures:

Primary outcome measures:

- Change in Mean K- value
- Thinnest corneal pachymetry

Measured by Pentacam Scheimplug imaging preoperatively and postoperatively after the procedure at 6 months of follow up.

Secondary outcome measures:

Complications associated with hypotonic corneal collagen crosslinking with respect to

I. Endothelial cell damage

II. infection

III. Stromal scars

MATERIALS AND METHODS

Study Design:

It is a prospective non randomized interventional study conducted at Aravind Eye Hospital, Madurai.

Duration:

Patients were recruited from July 2014 to January 2015 and will be followed up for a period of 6 months(+/- 15 days) till August 2015.

Source of data:

Cornea Services, Aravind Eye Hospital, Madurai

Sample size:

During this period from July 2014 to January 2015, all the patients who satisfy the inclusion criteria for enrollment will be recruited for the study. 21 patients were recruited for my study during this period out of which all the 21 patients were followed up in the immediate postoperative day until discharge, at 3months(+/- 15 days) and at 6months (+/- 15 days).

Inclusion Criteria:

1) Patients with progressive keratoconus (increase in astigmatism or myopia by 1 diopter or increase in K-Max by 1.50 diopter within the last 1 yr).

2) Age of study population between 10 to 25 years

3) Corneal pachymetry should be between 350 microns to 400 microns at the thinnest point

4) Healthy corneal endothelium

5) Feasability to come in the time frame specified for the study

Exclusion criteria:

1. Central or paracentral corneal opacities
2. H/O herpetic uveitis
3. Severe dry eyes and ocular surface disorders
4. Concurrent corneal infections
5. Preexisting autoimmune diseases
6. Pregnant or nursing women
7. Prior hormone therapy
8. Post refractive surgery patients

Diagnosis:

Diagnosis of the disease will be made by careful history, slit lamp evaluation and Pentacam Scheimplug imaging.

Parameters to be evaluated:

Preoperative:

- UCVA – (Using Snellens Visual Acuity Chart)
- BCVA
- Manifest Refraction
- Spherical Equivalent
- Vision with Contact lens
- IOP-(Measured by Non Contact Tonometry)
- Keratometry –(Measured by Pentacam Scheimplug Imaging)
- Corneal thickness at the thinnest point measured by(Pentacam Scheimplug imaging
- Endothelial count –(Konans Specular Microscopy)

Intraoperative Pachymetry(Using ultrasound pachymeter –PACSCAN)

Immediate postoperative period :

- Corneal Haze
- Days of Epithelial healing

3 months postop:

- UCVA
- BCVA
- Manifest Refraction
- Spherical Equivalent
- Vision with Contact lens
- IOP

6 month postop:

- UCVA
- BCVA
- Manifest Refraction
- Spherical Equivalent
- Vision with Contact Lens
- IOP
- Corneal Topography
- Specular Microscopy
- Corneal Thickness at the Thinnest Point

Informed consent:

An informed consent was taken from the patient after explaining the procedure and the outcome of the surgery in detail including the possibility of various complications in his or her own language. Patients were informed about the frequent follow-ups involved in the study. If the patient is a minor, consent was taken from the parents of the minor.

SURGICAL TECHNIQUE OF HYPOTONIC CORNEAL COLLAGEN CROSS LINKING:

Prerequisites before starting the procedure:

- Surgeon has to check the most recent Pentacam
- Minimal corneal thickness of 350 microns should be present

  Confirm the eye for treatment under LA/GA
- Prior to treatment the intended irradiance of 3 mw/cm^2 is calibrated using a UVA meter (2.7 to 3.3mw/cm^2) keeping the aperture size to "L"
- After calibration keep the aperture size to "M" and keep it ready for UV irradiance

Procedure:

- One drop of topical anaesthetic applied (4% lignocaine - Aurolig eye drops)

Subsequently one drop of topical moxifloxacin (0.5% Vigamox eye drops, Alcon Company) instilled. Eye is cleaned, draped and speculum applied .

Measure the preoperative corneal thickness

- Carefully remove the corneal epithelium from the centre for about 7-8mm with the help of Bard Parker handle with a 15 no. blade mounted on it.

Measure the corneal Thickness

- Place the limbal guard.Ensure that it covers the limbal area
- Distilled water is applied for 1st 10 minutes.

Measure the corneal thickness

- Hypotonic riboflavin 0.1% is applied over the cornea every 2 minutes for 20 minutes.

Measure the corneal thickness

- The UV unit is turned on. The standard instructions are followed. UVA irradiance is started for 30 minutes at a distance of 50mm.
- Switch of all the lights near the procedure table.
- During the procedure hypotonic riboflavin solution is applied every 2 minutes. Topical anaesthetic, reinstilled whenever needed.

Measure the corneal thickness

- After treatment thoroughly wash the cornea with saline.
- Apply topical antibiotic solution- moxifloxacin(0.5% Vigamox eye drops)

- Apply bandage contact lens
- Apply pad and bandage

Continue moxifloxacin eye drops 2nd hourly in the ward with oral analgesics if needed.

Postoperative Treatment:

Eye drops 0.5% moxifloxacin (Vigamox) eye drops QID for 1 month.

Follow up:

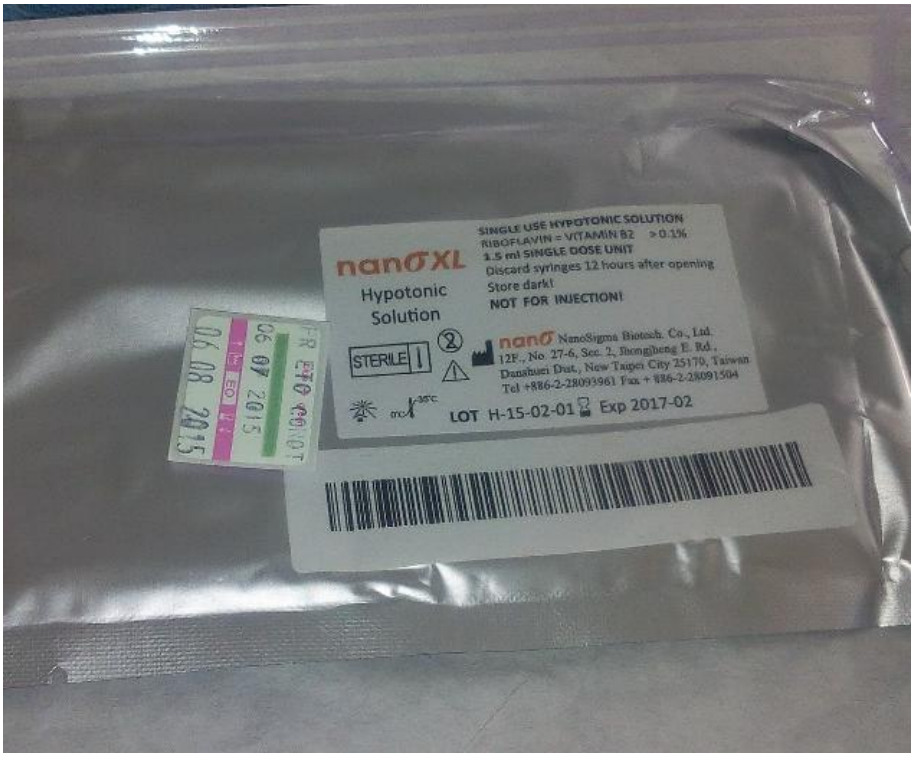
1.Immediate first postop day till the day when the epithelium heals.

2.3 Months.

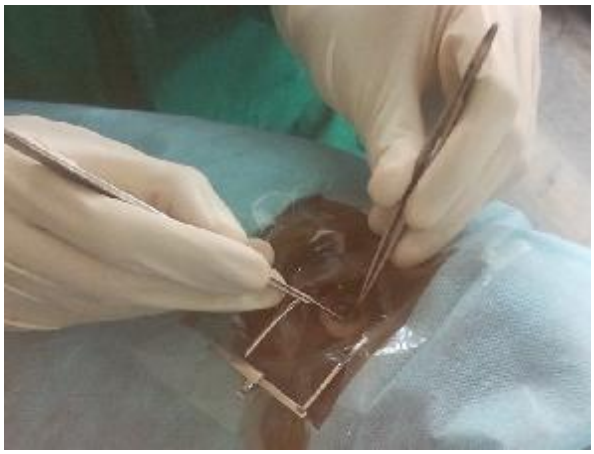
3.6 months.

All the necessary investigations were repeated at all follow up visits.

Hypotonic Riboflavin Solution



Hypotonic Riboflavin Assisted Corneal Collagen Crosslinking -Steps



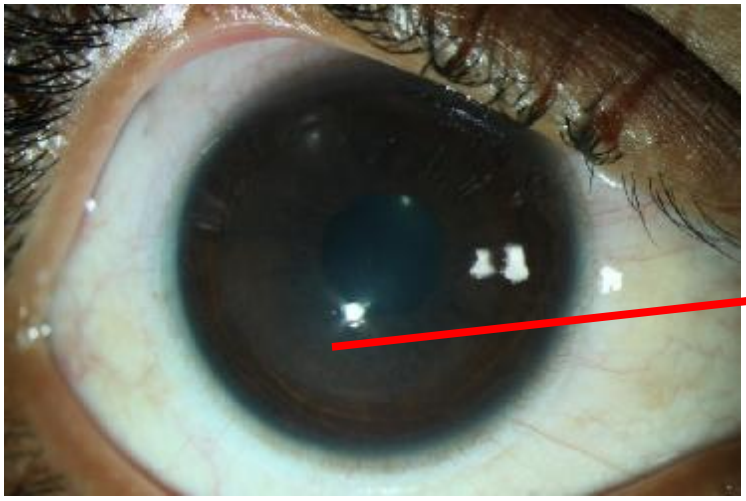
Epithelial Scrapping

Limbal Guard and Hypotonic Riboflavin Application

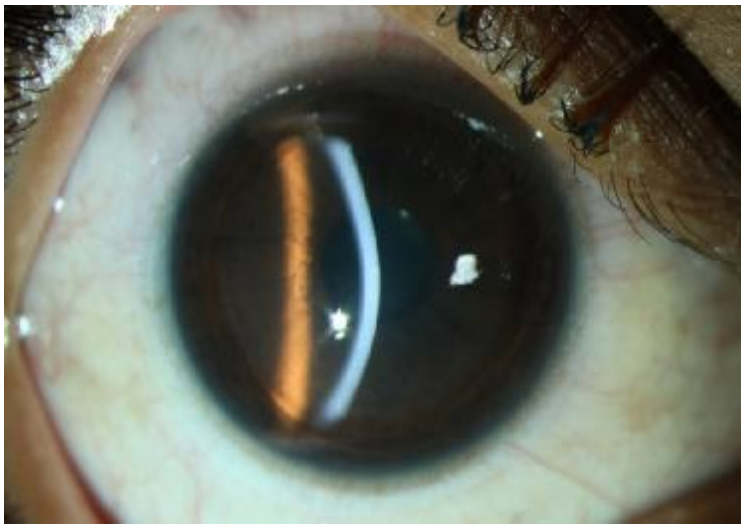
Irradiation with UV-A light @3mW/cm2

Intraoperative pachymetry

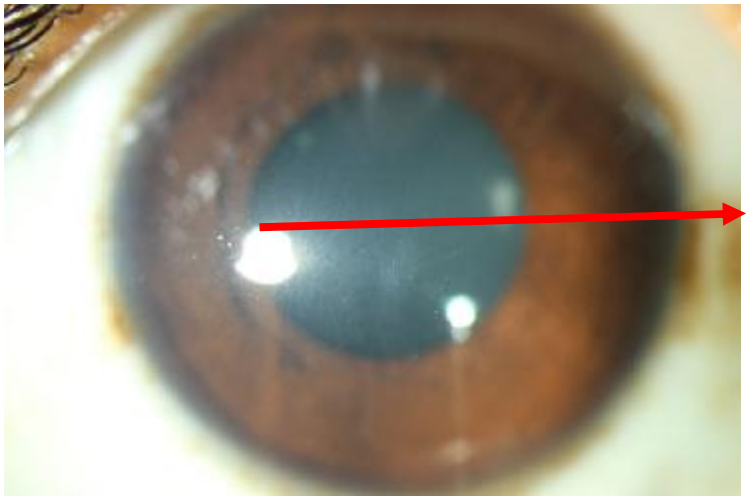
Three Months Postoperative Period Examination



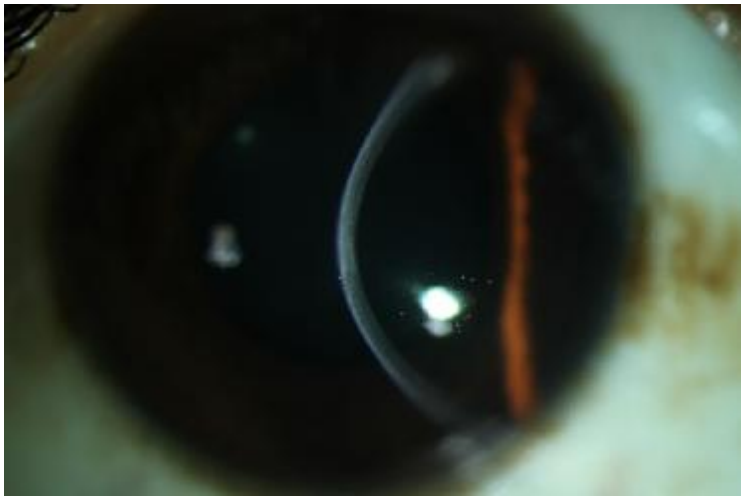
Stromal haze



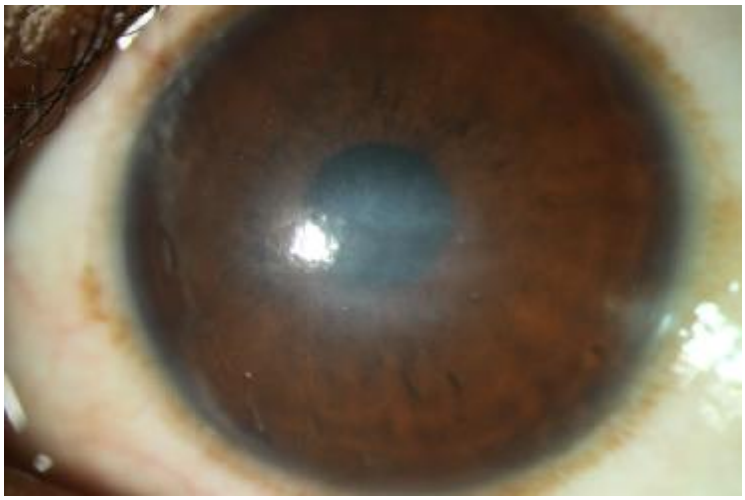
At Six Months Postoperative Period Examination



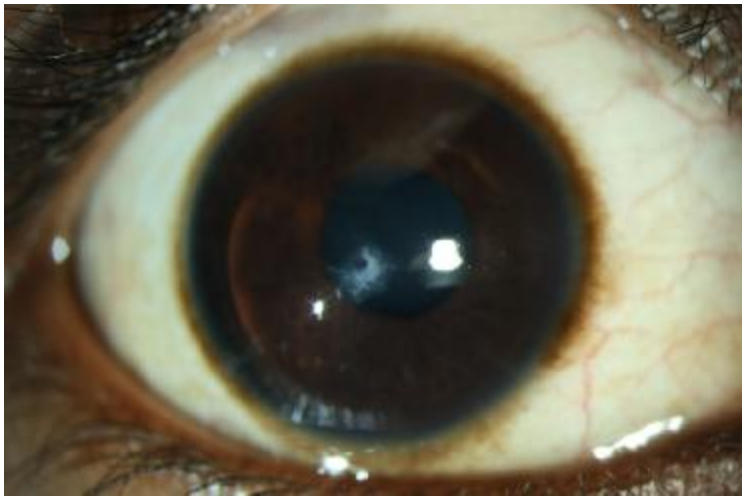
Stromal Haze



Persistent Stromal Haze -6 months follow up



Apical scarring -6 months follow up



OCULUS PENTACAM[40]

The Pentacam is a rotating Scheimpflug camera. The rotational camera generates Scheimpflug images in three dimensions, with the dot matrix fine-meshed in the center due to the rotation. Any subtle eye movement is detected by an another camera and corrected for in the process to some extent. The Pentacam calculates a 3-dimensional model of the anterior eye segment.

The topography and pachymetry of the entire anterior and posterior surfaces of the cornea from limbus-to-limbus are calculated and depicted. The anterior segment analysis includes the calculation of the chamber angle, chamber volume and chamber height and a manual measuring function at any location in the anterior chamber of the eye. The images of the anterior and posterior surface

of the cornea, the iris and the anterior and posterior surfaces of the lens are generated.

The lens densitometry is quantified. The Scheimpflug images taken during the examination are captured in the main unit and all image data are transferred to the personal computer. Once the examination is finished, the personal computer calculates a three dimensional model of the anterior eye segment, from which all additional information is derived.corneal thickness and elevation back and front

KONAN SPECULAR MICROSCOPY:

A specular microscope is a reflected light microscope. It works by projecting light onto the cornea and then imaging the reflected light from the optical interface between the corneal endothelium and the aqueous humor .

The reflected image is captured by the instrument and analysed to produce a magnified view of a small area of the cornea .This view facilitates the estimation of endothelial cell density and allows for an evaluation of endothelial cell morphology.

UV-X -TM ILLUMINATION SYSTEM VERSION 1000(IROC,SWITZERLAND)

It is a portable optical cum electronic device in which the light emitting diodes of the device produce UV-light at a wavelength of 365. Parts of the device :

1.Mechanical stand used to mount the UV-X light source on a stable table.

2.Power supply –A low voltage current is delivered to the light source with a DC cord

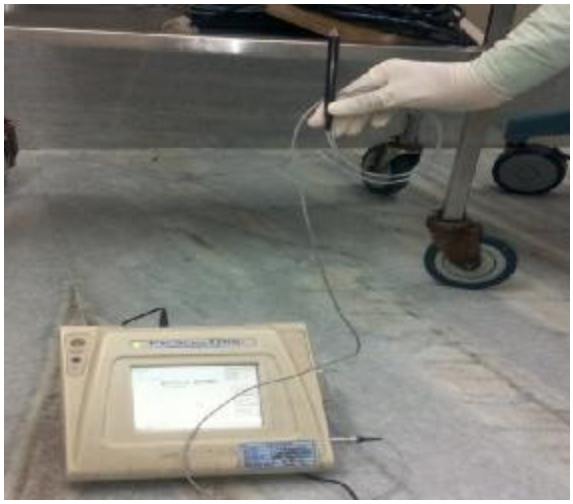
3.UV-X light source has a beam aperture of 25mm diameter. The treatment lane is about 50mm distance from the beam aperture. The aperture wheel controls the

diameter of the treatment plane. Three sizes of the aperture available are small(7.5mm),medium(9.5mm) and large (11.5mm).

4.UV light meter is used to check the correct UV light irradiation .

5.Sensor probe adapter attached to the UV light meter is mounted in the beam aperture. The optimum value of correct irradiance is 3.0+/-mw/cm^2 To start the device, it is first mounted on a table and the irradiation checked using the UV light meter. Then medium aperture(9.5mm) is selected and the device is switched on. The beam is kept at a distance of 50mm from the cornea. Then the UV radiations at the appropriate dosage is given for half an hour and the device automatically gets switched off after 30 minutes.

PACSCAN 300P Pachymeter:[38]



The PACSCAN™ series is the latest generation ophthalmic biometry instruments introduced by Sonomed.

PACSCAN™ 300P. This Pachymeter system allows measurement and mapping of corneal thickness with the placement of the pachymeter probe against a patient eye, an ultrasound image can be obtained and converted into a corneal thickness measurement.The displayed measurement can be stored within the system's memory at a corresponding location on the corneal map.

Procedure

1. Be sure the probe tip is clean & dry.

2. Place the tip of the probe onto the cornea starting at the optical center, making certain that the tip is perpendicular to the surface of the cornea.

3. Press the foot pedal or touch the “start” button to perform the measurement process.

4. After the completion of an acceptable measurement, the average reading will be displayed on the screen along with the standard deviation. Also displayed in the upper part of the screen will be the average and standard deviation for the cumulation of readings.

STATISTICAL ANALYSIS

The data was recorded on a simple self designed proforma and then transferred to the excel sheet taking care all the entries made in the excel sheet were correct and appropriate for statistical analysis. All the quantitative variables were assessed for normal distributions.

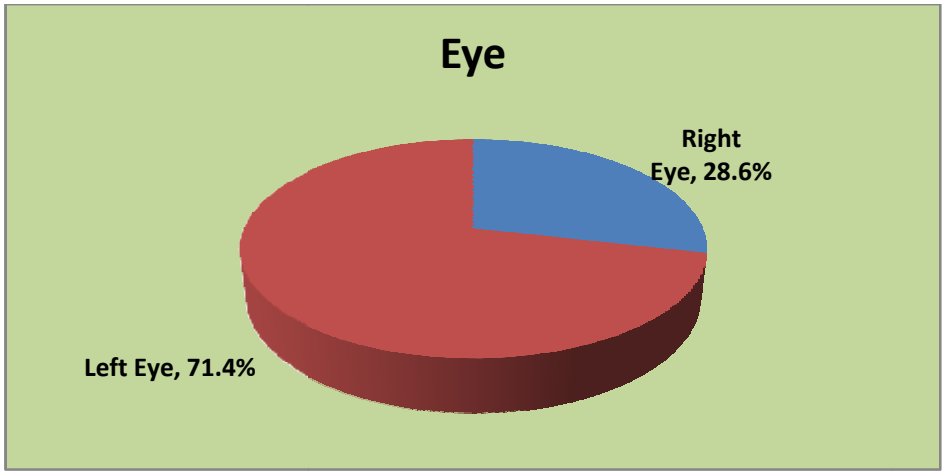
Mean (SD) or Frequency (Percentage) was used to describe summary information. Student's t-test (if data is normal) or Wilcoxon signed rank sum test (if data is non-normal) was used to assess the difference of continuous variable. P-value is less than 0.05 considered as statistically significant. All statistical analysis was done by STATA 11.1 (Texas, USA).

OBSERVATIONS AND RESULTS

A total of 21 eyes of 21 patients with preoperative thinnest pachymetry measured by Pentacam Scheimplug imaging < 400 microns were included in our study as per the study protocol to analyse the safety and efficacy of hypotonic corneal collagen crosslinking. The demographic profile of the patients included in the study is summarized below.

Chart.1

EYE



Among the 21 eyes considered for our study 6 were right and 15 were left.

AGE

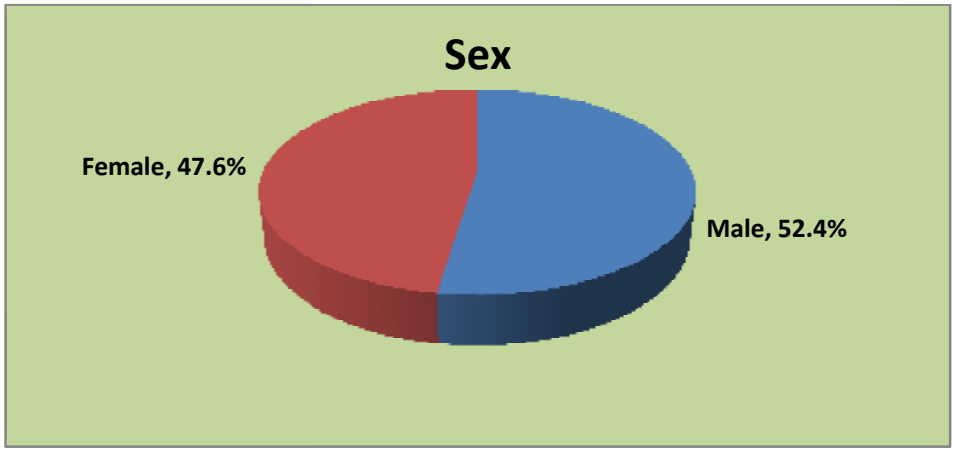
The Mean age of the patients who underwent hypotonic corneal collagen crosslinking was 17.5 years with the age range was 10 – 25 years.

Table 1. SEX DISTRIBUTION

Gender

Gender	N=21	%
Male	11	52.4
Female	10	47.6
Total	21	100

Chart2.



A total of 21 patients were enrolled in the study, 11 were males and 10 were females .

Table 2.

PREVIOUS OCULAR HISTORY

Previous Ocular History	n	%
CL	4	19.0
Glasses	2	9.5
VKC	4	19.0
Nil	11	52.4
Total	21	100.0

Based on the previous ocular history findings Only 10 of the 21 patients had previous ocular history. Remaining 11 patients had no significant previous history. History of contact lens use was present in 4 patients. History of Vernal Keratoconjunctivitis was present in 4 of the patients and history of glass use was present in 2 patients.

Visual Acuity:

Visual acuity was recorded by Snellen's chart for all the patients on all the visits. For the ease of comparison visual acuity was converted to logMAR Snellen visual acuity.

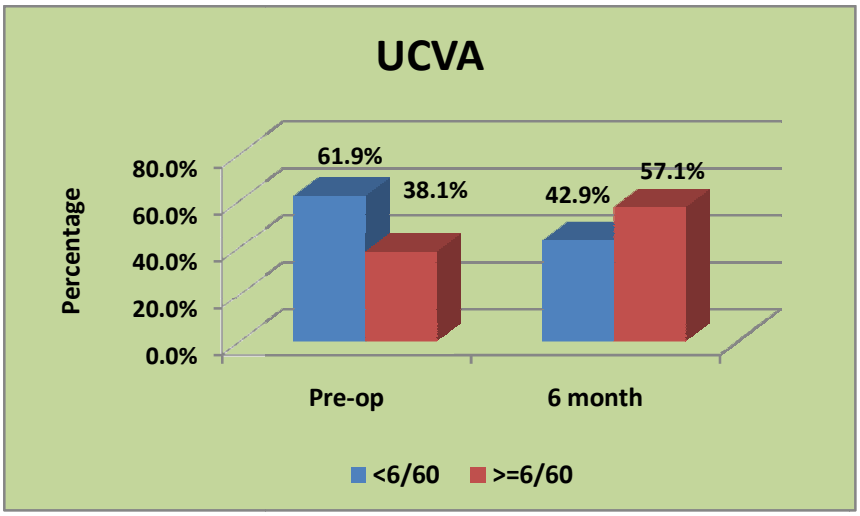
Table 3.logMAR VISUAL ACUITY :

logMAR Visual Acuity	**N**	**Median**	**Mean (Mean ±SD)**	**Range**	**P - value***
UCVA					
Pre-op	21	1.08 (5/60)	1.08(±0.23)	6/36 - 2/60	-
1 month	21	1 (6/60)	1.01(±0.18)	6/36 - 3/60	0.2278
6 month	21	1 (6/60)	0.99(±0.24)	6/12 - 2/60	0.1826
BCVA					
Pre-op	21	0.48 (6/18)	0.41(±0.21)	6/6 - 6/36	-
1 month	21	0.48 (6/18)	0.38(±0.22)	6/6 - 6/36	0.1924
6 month	21	0.18 (6/9)	0.26(±0.28)	6/6 - 6/36	0.0337
With contact lens					
Pre-op	19	0 (6/6)	0.08(±0.12)	6/6 - 6/12	-
1 month	15	0 (6/6)	0.03(±0.09)	6/6 - 6/12	0.3173
6 month	17	0 (6/6)	0.06(±0.11)	6/6 - 6/12	0.6331

***Wilcoxon Signed Rank Test**

Chart 3.

UNCORRECTED VISUAL ACUITY

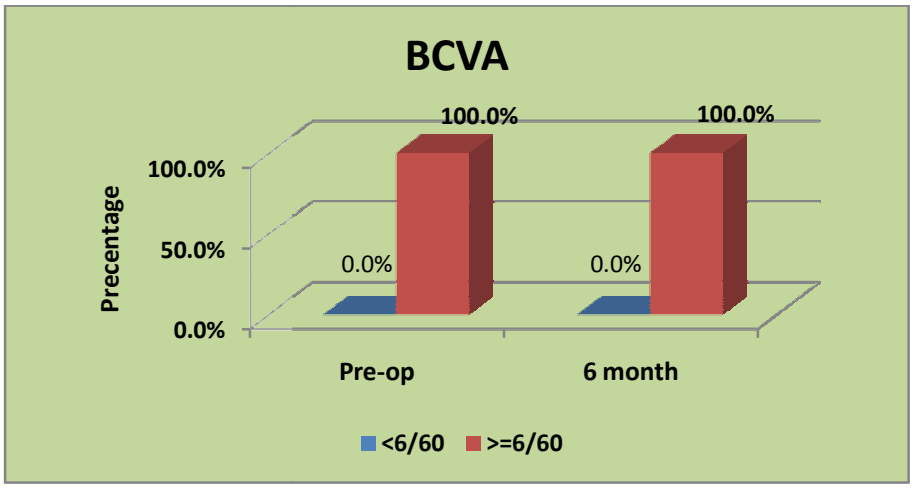


The mean Snellen logMAR UCVA (mean$\pm SD$) in the eyes that underwent hypotonic CXL was 1.08($\pm$0.23) preoperatively, 1.01($\pm$0.18) at 3 months, 0.99($\pm$0.24) at 6 months. There was no statistically significant change with respect to preoperative uncorrected visual acuity and final visual acuity at 6 months.

Preoperative Uncorrected Visual Acuity worse than 6/60 was 61.9%where as at 6 months of postop, the percentage of patients with Uncorrected Visual Acuity worse than 6/60 had reduced to 42.9%. Similarly the percentage of patients with preoperative Uncorrected visual acuity better than 6/60 was 31.8% whereas at 6 months of followup the percentage of patients with Uncorrected visual acuity better than 6/60 had increased to 57.1%.

Chart 4.

BEST CORRECTED VISUAL ACUITY



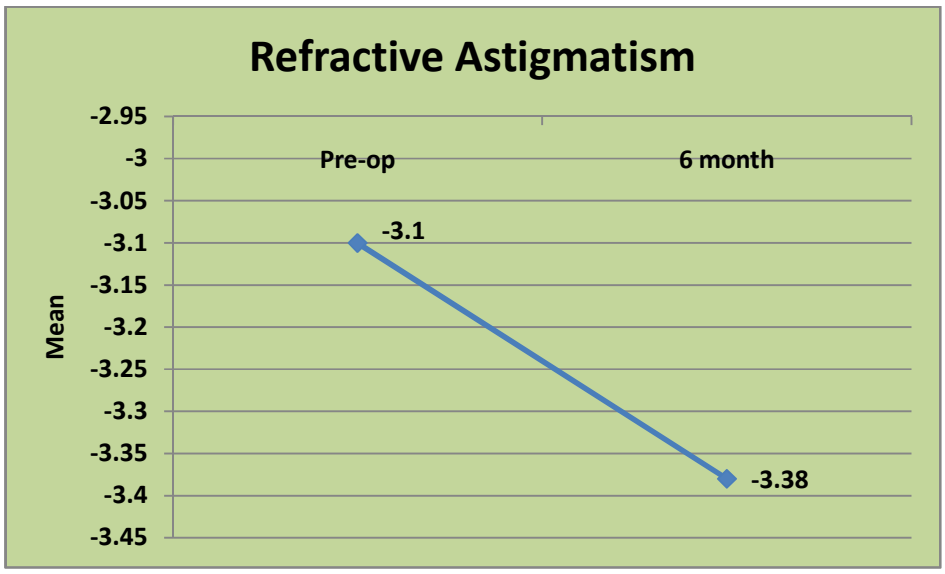
The mean Snellen logMAR BCVA (mean$\pm SD$) in the eyes that underwent Hypotonic CXL was 0.41($\pm$0.21) preoperatively, 0.38($\pm$0.22) at 3 months and 0.26($\pm$0.28) at 6 months .There was a significant improvement in the BCVA among the patients at final followup at 6months (p value=0.03 37).

Table 4.

REFRACTIVE ASTIGMATISM

Parameters	n	Mean(SD)	Range	P - value*
Cylinder				
Pre-op	21	-3.10($\pm$2.4)	-6, 6	-
1 month	21	-3.40($\pm$1.1)	-6, -1.5	0.6084
6 month	21	-3.38($\pm$1.3)	-6, -1.5	>0.999

Chart 5:



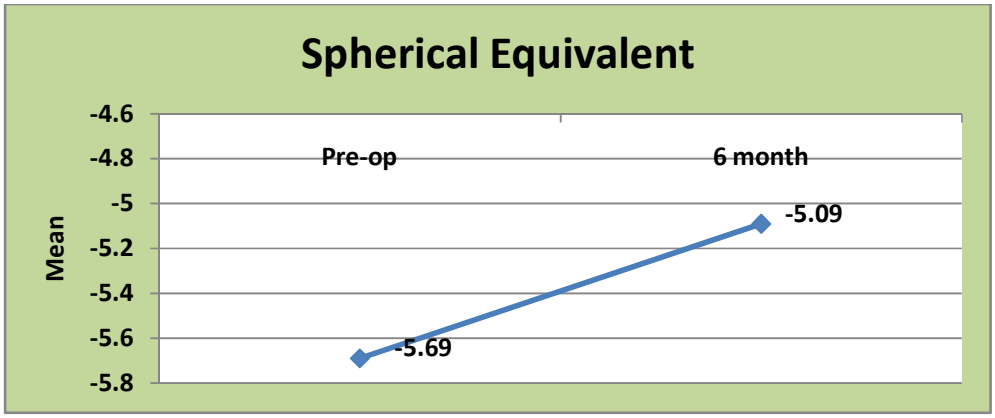
The mean refractive astigmatism (mean$\pm SD$) in the eyes that underwent hypotonic CXL procedure -3.1D($\pm 2.4D$) preoperatively,-3.4D($\pm 1.1D$) at 3 months and -3.38D ($\pm 1.3D$)at 6 months postoperatively. There was no significant decrease in the refractive astigmatism.

Table 5.

SPHERICAL EQUIVALENT

Parameters	n=21	Mean(SD)	Range	P - value*
Spherical equivalent				
Pre-op	21	-5.69(±4.67)	-18.75, 1.25	-
1 month	21	-5.08(±3.96)	-15, -1.5	0.4094
6 month	21	-5.09(±3.96)	-14.5, -0.75	0.8049

Chart 6.



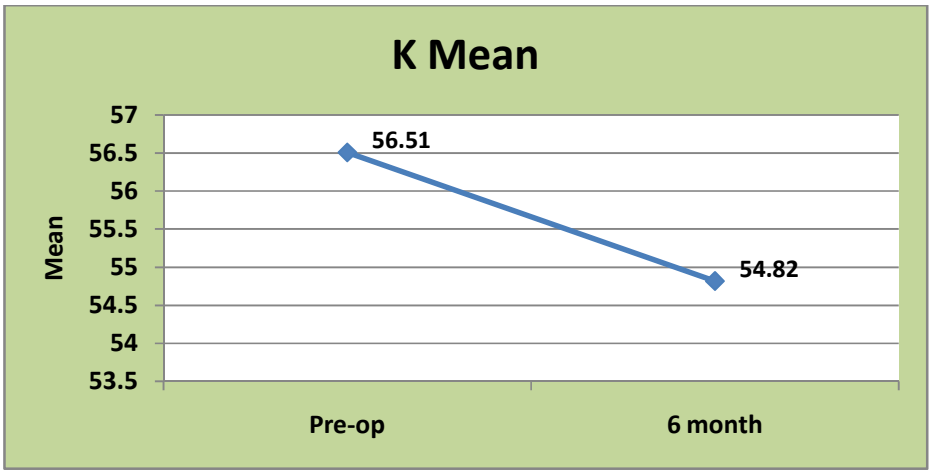
The mean Spherical equivalent (mean $\pm SD$) in the eyes that underwent hypotonic CXL was -5.69D (±4.67D) preoperatively,-5.08D (±3.96D) at 3 months and 5.09D (±3.96D) at 6 months . There was no significant reduction in the spherical equivalent in the cases.

Table 6.

K –MEAN

Parameters	n=21	Mean(SD)	Range	P - value*
K mean, *in Dioptres*				
Pre - op	21	56.51D(±5.3)	47 - 68.3	
6 month	21	54.82D(±5.9)	45.4 - 65.7	0.0070

Chart 7.



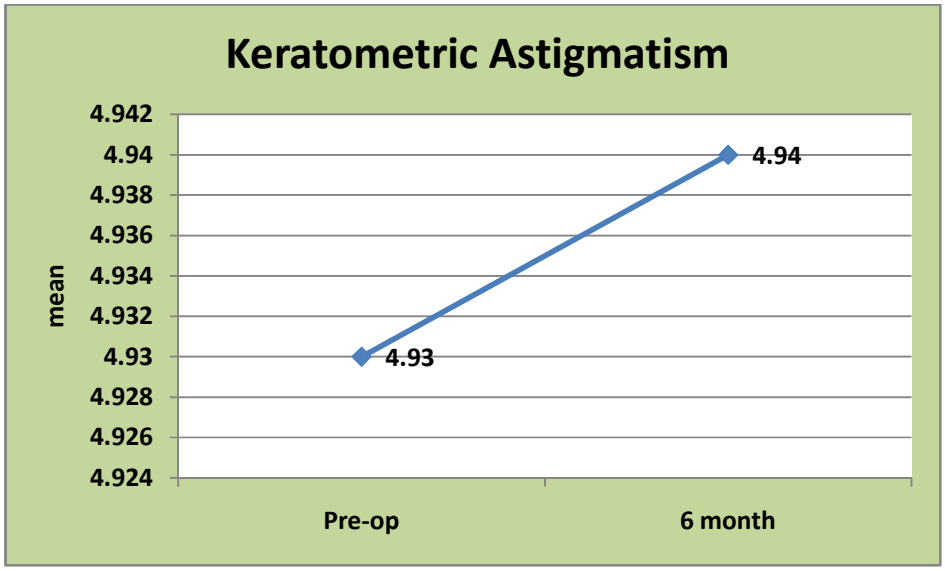
The K-mean in the eyes that underwent hypotonic CXL was 56.51D(±5.3D) preoperatively and 54.82D (±5.9D) at 6 months postoperatively.There was a significant decrease in K-mean at 6 months of follow up(p=0.0070).

Table 7.

KERATOMETRIC ASTIGMATISM

Parameters	n	Mean(SD)	Range	P - value*
Astigmatism, *in Dioptres*				
Pre-op	21	4.93D(±2.5)	0.1 - 10.4	
6 month	21	4.94D(±2.4)	1.6 - 10.4	0.9032

Chart 8.



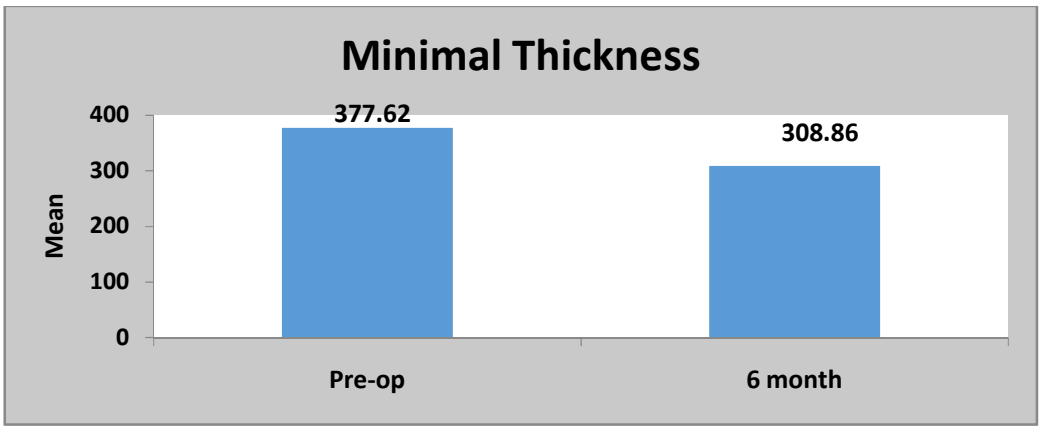
The mean keratometric astigmatism (mean$\pm SD$) among the patients who underwent hypotonic CXL was 4.93D($\pm 2.5D$)preoperativey and 4.94D($\pm 2.4D$) at 6 months of follow up.There was no significant change in the keratometric astigmatism from the preoperative value to at 6 months postop(p=0.9032).

Table 8.

THINNEST PACHYMETRY

Parameters	N	Mean(SD)	Range	P - value*
Minimal Thickness, *in μm*				
Pre-op	21	377.62($\pm$13.8)	350 - 396	
6 month	21	308.86($\pm$48.5)	174 – 355	0.0001

Chart 9.



Mean thinnest pachymetry (mean $\pm SD$) in the eyes that underwent hypotonic CXL was 377.62 ($\pm$13.8) microns preoperatively and at 6 months of final follow up it was 308.86($\pm$48.5) microns .There was a significant decrease in corneal pachymetry in the eyes that underwent hypotonic CXL with respect to preoperative pachymetry and at 6 months of final follow up.

Table 9.

SPECULAR MICROSCOPY

Parameters	n	Median	Mean(SD)	Range
Cell Count				
Pre-op	10	2850	2770.30(190.0)	2387 – 2915
6 month	15	2667	2723.13(370.4)	2119 – 3717
Hexa				
Pre-op	10	45	46.4(10.3)	34 – 69
6 month	15	38	37.0(7.1)	22 – 52
Coefficient Variation				
Pre-op	10	41.5	43.20(6.2)	36 – 54
6 month	15	47.0	48.93(9.2)	37 – 73
SD				
Pre-op	10	151.5	167.40(41.4)	129 -248
6 month	15	179.0	186.33(39.5)	120 -253

There was no significant change in the specular count of the eyes that could be measured preoperatively and at 6 months of postoperative follow up. However the values could not be captured due to advanced stage of the disease in many of the eyes the inability to capture the images or values were also due to the postoperative stromal haze and nebular opacities in some cases. This was one of the major limitations of the study.

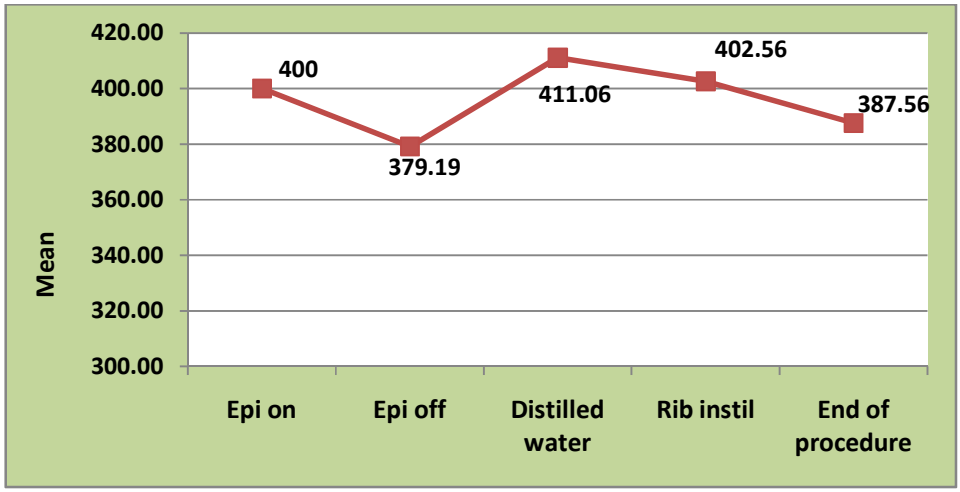
Table 10.

INTRAOPERATIVE PACHYMETRY

	N=16	Mean(SD)	Range	P-value
Epi on	16	400.00(14.09)	374 - 422	-
Epi off	16	379.19(15.17)	355 - 404	-
Distilled water	16	411.06(21.70)	381 - 470	-
Rib-instil	16	402.56(23.92)	368 - 448	-
End of procedure	16	387.56(33.08)	360 - 470	0.192

Chart 10.

INTRAOPERATIVE PACHYMETRY



The mean intraoperative pachymetry was 400(±14.09) microns epithelium on, 379.19(±15.17) microns epithelium off, 411.06(±21.70) microns with

distilled water 387.56(±33.08) microns at the end of the procedure. There was an increase in the stromal thickness following the instillation of distilled water followed by hypotonic riboflavin after epithelial debridement but it was not significant .

Days of Epithelial Healing

The Median days of epithelial healing was 3 days and healing time ranged between 3 -7 days .

Table 11.

Postoperative Stromal Haze (Immediate Post-op)

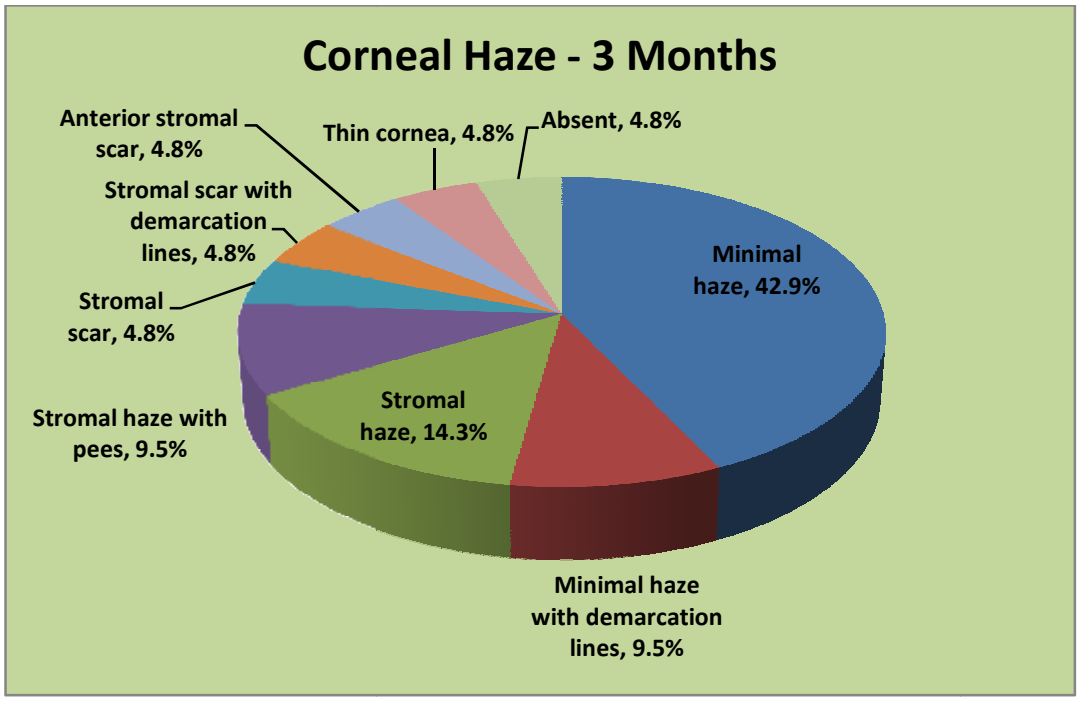
Stromal Haze	**N=21**	**%**
Present	20	95.2
Stromal Infiltrate	1	4.8
Total	21	100

In the immediate postoperative day among the 21 eyes, 20(95.2%) eyes that had underwent hypotonic CXL procedure showed stromal haze and 1(4.8%) eye reported with a stromal infiltrate which was aggresively treated with appropriate antibiotics which allowed healing of the infiltrate with a delay in epithelial healing by 7 days.

Table 12.
Postoperative Corneal Haze - 3month

Corneal Haze	**N=21**	**%**
Minimal haze	9	42.9
Minimal haze with demarcation lines	2	9.5
Stromal haze	3	14.3
Stromal haze with pees	2	9.5
Stromal scar	1	4.8
Stromal scar with demarcation lines	1	4.8
Anterior stromal scar	1	4.8
Thin cornea	1	4.8
Absent haze	1	4.8
Total	21	100.0

Chart 11.



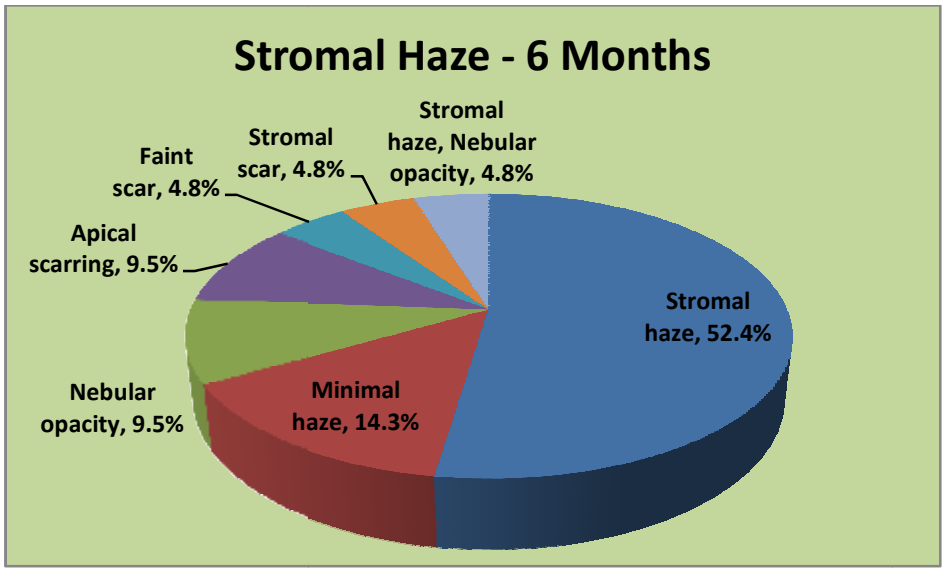
At the third postoperative month among the 21 eyes that underwent hypotonic CXL procedure 16(76.2%) eyes had stromal haze, 3 eyes (14.4%) eyes had stromal scar, thin cornea was present in 1(4.8%) of the eyes and stromal haze was absent in 1(4.8%) of the eyes.

Table 13.

Postoperative Stromal haze (6month)

Stromal haze	**N=21**	**%**
Stromal haze	11	52.4
Minimal haze	3	14.3
Nebular opacity	2	9.5
Apical scarring	2	9.5
Faint scar	1	4.8
Stromal scar	1	4.8
Stromal haze, Nebular opacity	1	4.8
Total	21	100.0

Chart 12.



At 6 months of postoperative follow up 14 (66.7%) eyes had stromal haze , 3(14.3%) eyes had nebular opacity and 4(19.1%) eyes had stromal scar.

DISCUSSION

DEMOGRAPHIC RESULTS :

This was a prospective non randomized interventional study undertaken to evaluate the safety and efficacy of hypotonic corneal collagen cross linking in thin keratoconic corneas less than 400 microns .

The mean age of presentation is 17.52 ($\pm$4.11) years and it ranged between 10 to 25 years. Among a total of 21 patients enrolled in the study 11 were males (52.4%) and 10 were females (47.6%).In a study by Freiderick Raiskup and Spoerl,[28] 29 patients were enrolled for the study 20 were males and 9 were females with a mean age of 27.4 $\pm$ 9.4years.

VISUAL ACUITY:

In the uncorrected visual acuity, no significant improvement was observed at 6 months of follow up. However we found significant improvement in the best corrected visual acuity at 6 months of follow up by 0.26($\pm$0.28)logMAR units. The improvement in the best corrected visual acuity is due to the reduction in the keratometry and astigmatism as suggested by the previous studies.

In a Study conducted by **Wollensak et al** [20] in 23 eyes, the BCVA improved by 1.26 lines in 65% of the patients.

A study conducted by **Caporrosi et al** showed an improvement in UCVA by 3.6 lines and 1.66 for BCVA at 6 months .

Vinciguerra et al [38] conducted a study on 28 eyes which showed a mean increase in logMar UCVA from o.77(±0.18) to 0.51(±0.20) at 6 months and 0.57(± 0.16) at 12 months and logMAR BCVA from 0.28(±0.09) to 0.17(±.11) at 6 months and 0.14 (±0.08) at 12 months.

In a study by **Raiskup and Eberhard Spoerl** [28] on 32 eyes the mean BCVA at the time of treatment was 0.63(±0.37)logMAR and at 1 year after treatment this value was not statistically different with BCVA of 0.59(±0.42) logMAR(p=0.662).

REFRACTIVE RESULTS :

In our study there has been no mean decrease in refractive astigmatism from preoperative values to at 6 months of postoperative follow up.

Wollensak et al [17] noted a significant increase in the corneal rigidity by increase in the stress by 71.9% in the porcine enucleated corneas and by 328.9% in human enucleated corneas.

Frederick Raiskup and Eberhard Spoerl [28] in their evaluation of thin keratoconic corneas that were treated with hypotonic riboflavin solution and UVA assisted CXL showed a mean BCVA at the time of intervention,0.63(± 0.37) logarithm of minimal angle of resolutionand at 1 year of treatment this

value was not statistically significant 0.59 (±0.42) logarithm of minimal angle of resolution (P=0.662).

Aleksander Stojanovic et al [36] in their contralateral study of corneal collagen cross linking with and without epithelium removal with hypotonic riboflavin solution in patients with bilateral progressive keratoconus was randomly treated with epithelium on (Group 1) CXL with hypotonic riboflavin solution in one eye and the fellow eye of the patients were subjected to epithelium off CXL(Group 2) with hypotonic riboflavin solution. 65% of the eyes in group 1 and 25% of the eyes of group 2 had 2 more lines of improvement in visual acuity. The mean spherical equivalent and the refractive cylinder remained stable compared to preoperative status throughout the 12 month follow up period. No significant difference in visual acuity or refraction measurements were found in the 2 groups.

KERATOMETRY :

In our study there has been a reduction in the mean keratometry by + 1.69D from the preoperative values to 6 months postoperatively. Before surgery the mean K was 56.51D (±5.3D) and 6 months after surgery it was 54.52D (±5.9D). Flattening effect of the cornea following hypotonic crosslinking is similar to other studies.

In a study conducted by **Hafezi et al** [29] in 2009 on 20 patients with progressive keratoconus with thin corneas treated with a modified technique of corneal collagen crosslinking with hypotonic riboflavin scheimpflug analysis of the maximum K readings showed no progression of the keratectasia (Kmax≥ +1.0 D); stabilization of the keratectasia was observed in 12 patients and regression, in 8 patients (Kmax≥+1.0 D).

In another study conducted by **Frederick Raiskup and Eberhard Spoerl** [28] in 2011 evaluated the 1 year results of keratoconic eyes with thin corneas that were treated with hypotonic riboflavin solution and UVA light. The results of the study showed the mean K value from the apex of the keratoconus was 65.6D(±11.2D) and 1 year after the treatment this value was maintained at 64 D(±11.0 D) with a p value (p=0.839).

In another study conducted by **Prema Padmanabhan and Abishek Dave**[39] in 2013 in their study on evaluating the efficacy of collagen crosslinking in thin corneas with hypotonic riboflavin solution. Fifty eyes that underwent hypoosmolar CXL were compared with 50 eyes that underwent isoosmolar (standard) CXL in the same period. At 1 year follow-up, the steepest keratometry (Pentacam) had decreased by an average of 0.88 (± 2.26 D) in the isoosmolar group and 0.18 (± 3.23 D) in the hypoosmolar group.

Thinnest pachymetry:

Mean thinnest pachymetry (mean $\pm SD$) in the eyes that underwent hypotonic CXL was 377.62 ($\pm$13.8) microns preoperatively and at 6 months of final follow up it was 308.86($\pm$48.5)microns. There was a significant decrease in corneal pachymetry in the eyes that underwent hypotonic CXL with respect to preoperative pachymetry and at 6 months of follow up.

Aleksander stojanovic et al [29] in his study to compare the safety and efficacy of "epithelium on" CXL and "epithelium off CXL" with hypotonic riboflavin solution evaluated the thinnest corneal pachymetry postoperatively in both the groups .They observed a decrease in thickness at 1 month follow up with a gradual increase in thickness in both the groups .However the thickness of the corneas in the first group increased to the preoperative level by the 1 year follow up (p=.273),whereas the thickness of the corneas measured from the second group remained thinner than that measured preoperatively(p=0.019).

INTRAOPERATIVE PACHYMETRY:

The mean intraoperative pachymetry (mean $\pm SD$) was 400($\pm$.09) microns with epithelium on,379.19($\pm$15.17)microns epithelium off,411.06($\pm$21.70)microns with distilled water instillation,402.56($\pm$23.92)microns with hypotonic riboflavin and 387.56($\pm$33.08)microns at the end of the procedure.There was a an increase in

the stromal thickness following the instillation of distilled water followed by hypotonic riboflavin after epithelial debridement but it was not significant. There are some of the studies to support this observation.

In a study conducted by **Hafezi et al**[30] CXL with hypotonic Riboflavin in thinner corneas found that the minimum corneal thickness before corneal abrasion measured and after corneal abrasion were measured as 398 microns and 323 microns respectively, which increased slightly to 330 microns after the application of isotonic riboflavin. After application of hypoosmolar riboflavin solution for ten minutes, the stromal thickness increased to 410 microns .

There was a distinct interindividual variation in the stromal swelling response and the amount of swelling from 3 minutes to 20 minutes . Most of the cases repeated application of the hypoosmolar solution followed by ultrasound pachymetry was needed to obtain a minimal stromal thickness of atleast 400 microns. In this study they could not conclude whether age, sex, or the underlying condition influenced the variation in the amount of stromal swelling.

Kaya et al [32] in 2011 studied the intraoperative corneal thickness measurements during collagen cross linking with hypoosmolar riboflavin solution.In their study of 9 eyes of 9 patients with progressive keratoconus and pellucid marginal degeneration the thinnest pachymetry readings were noted between 331 and 399 microns after epithelial debridement which decreased

significantly after the application of isoosmolar riboflavin solution for half an hour and increased significantly thereafter after hypoosmolar riboflavin application for ten minutes. This swelling produced was transient and the thinnest pachymetry readings decreased significantly after 10 and 30 minutes of isoosmolar riboflavin application compared with the thickness at the end of hypotonic riboflavin application. The conclusion of the study was swelling effect of hypotonic riboflavin might be short acting and not durable throughtout the procedure.

Raiskup and Ebarhard Spoerl [28] in 2011 in their study to evaluate the efficacy of hypotonic riboflavin on thin keratoconic corneas. According to their observation before the procedure the mean corneal thickness including the epithelium was 382.0 (±41.9) microns and the thickness further reduced to 337(±51.9) microns after the removal of the epithelium and the thickness increased to 451.8 (±46.7) microns after the application of hypotonic riboflavin solution

SPECULAR MICROSCOPY :

There was no significant change in the specular count of the eyes that could be measured preoperatively and at 6 months of postoperative followup. However the values could not be captured due to advanced stage of the disease in many of the eyes The presence of postoperative stromal haze and stromal

opacities were also one of the factors for poor measurement of values .This was one of the major limitations of the study.

STROMAL HAZE AND COMPLICATIONS OF THE PROCEDURE:

Days of Epithelial Healing

The Median days of epithelial healing was 3 days and it ranged between 3 to 7days.In the immediate postoperative period among the 21 eyes, 20(95.2%) eyes that had underwent hypotonic CXL procedure showed stromal haze and 1(4.8%) eye reported with a stromal infiltrate which was aggresively treated with appropriate antibiotics which allowed healing of the infiltrate with a delay in epithelial healing by 7 days.

At the third postoperative month among the 21 eyes that underwent hypotonic CXL procedure 16(76.2%) eyes had stromal haze, 3 eyes (14.4%) eyes had stromal scar ,thin cornea was present in 1(4.8%) of the eyes and stromal haze absent in 1(4.8%) of the eyes.

At 6 months of postoperative follow up 14 (66.7%) eyes had stromal haze, 3(14.3%) eyes had nebular opacity and 4(19.1%) eyes had stromal scar.

Naoko Kato et al [35] 2012 reported three cases with deep stromal opacity which occurred several months after collagen crosslinking with hypotonic riboflavin. In all the cases there was no delay in the epithelium healing. A mild stromal infiltration was present in a few days after the procedure however the

inflammation resolved in a weeks time. Cornea did not reveal any stromal opacity upto one month postop. But a deep stromal opacity that extended to the inferior paracentral area developed after a few months and persisted for nearly an year. As it was not present in the visual axis, the vision was not affected.The postoperative inflammation would have played a crucial role in its pathogenesis. Careful selection of the patient and sufficient use of the steroid to reduce the postoperative inflammation was needed.

Farhad Hafezi in 2011 reported a case failure of corneal collagen cross linking for progressive keratoconus after preoperative stromal swelling with hypotonic riboflavin solution in an extremely thin cornea with a minimal thickness after abrasion being 268 microns. Conclusion of the study was a minimal stromal thickness of atleast 330 microns should be available for effective crosslinking .

LIMITATIONS OF OUR STUDY

1. The sample size of our study was a small number only 21 eyes could be studied and so the interpretation of the results could vary from other studies
2. Specular microscopy could not be performed for some of the patients pre operatively and in some cases postoperatively due to advanced stage of the disease or due to stromal haze and scars postoperatively in some cases and therefore proper preoperative and postoperative comparison of the endothelial count could not be assessed.
3. Long term follow up is required to assess the efficacy of the procedure. Follow up period of 6 months was one of the shortcomings of the study.

CONCLUSION

Hypotonic Corneal collagen cross linking is relatively a safe and effective procedure in arresting the progression of keratoconus in thin corneas with thinnest corneal pachymetry between 350 to 400 microns.

Inspite of the presence of persistent stromal haze which is only an exaggerated form of stromal demarcation line as reported in some studies and with a few subjects reported with scaring and nebular opacity ,they did not affect the visual outcome of the subjects.

However still long term follow up studies of the keratoconus patients with thin corneas with a larger sample size is needed to assess the stability or regression of K- mean and also to study the disappearance or peristence of stromal haze and whether its presence had its effect on the visual outcome of the patients treated with hypotonic CXL.

Other alternative methods of assessing the endothelial cell health are needed apart from specular microscopy in cases of advanced stages of keratoconus and in the presence of postoperative stromal haze or stromal opacities.

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PROFORMA

Serial No:	Date :
Name:	Age /Sex:
MR No:	Date of Surgery:
Address:	Phone No:
Diagnosis	
Study Eye	

Previous Ocular History:

- H/O Vernal keratoconjunctivitis /allergy (chronic)
- H/O contact lens use Yes /No (H/O intolerance inappropriate fit)
- H/O glasses
- H/o previous ocular surgery Post C3R/Post lasik/Post intacs /None

Systemic History: Duration

Diabetes Mellitus Yes /No

Hypertension Yes /No

Collagen Vascular Disorder Yes/No

Slit Lamp Examination :

Slit lamp examination Preoperative	Slit lamp Post operative	Immediate Postoperative	3 Months Postop	6 Months postop
	Days of epithelial healing			
	Stromal haze			
	Others			

Intraoperative Pachymetry:

Hypotonic C3R Procedure	Intraop Pachymetry
Epithelium on	
Epithelium off	
After Instillation of Distilled water	
After instillation of Hypotonic Riboflavin	
End of the Procedure	

Intraocular Pressure:

Intraocular Pressure	Pre operative	At 3 months	At 6 months

Fundus :

Fundus	Preoperative	At 3 Months	At 6 months

Visual Parameters:

Visual parameter	Preoperative	At 3 months	At 6 months
UCVA			
BCVA			
Manifest Refraction			
Spherical Equivalent			
Vision with Contact Lens			

Keratometry:

Keratometry	Preoperative	6 Months Postop
K-Mean		
Astigmatism		
Thinnest corneal Pachymetry		

Specular Microscopy :

Endothelial count	Preoperative	6 Months Postoperative
Endothelial cell count		
% of Hexagonality		
Coefficient of Variation		
Standard Deviation		

Surgical Details :

Date of Surgery :

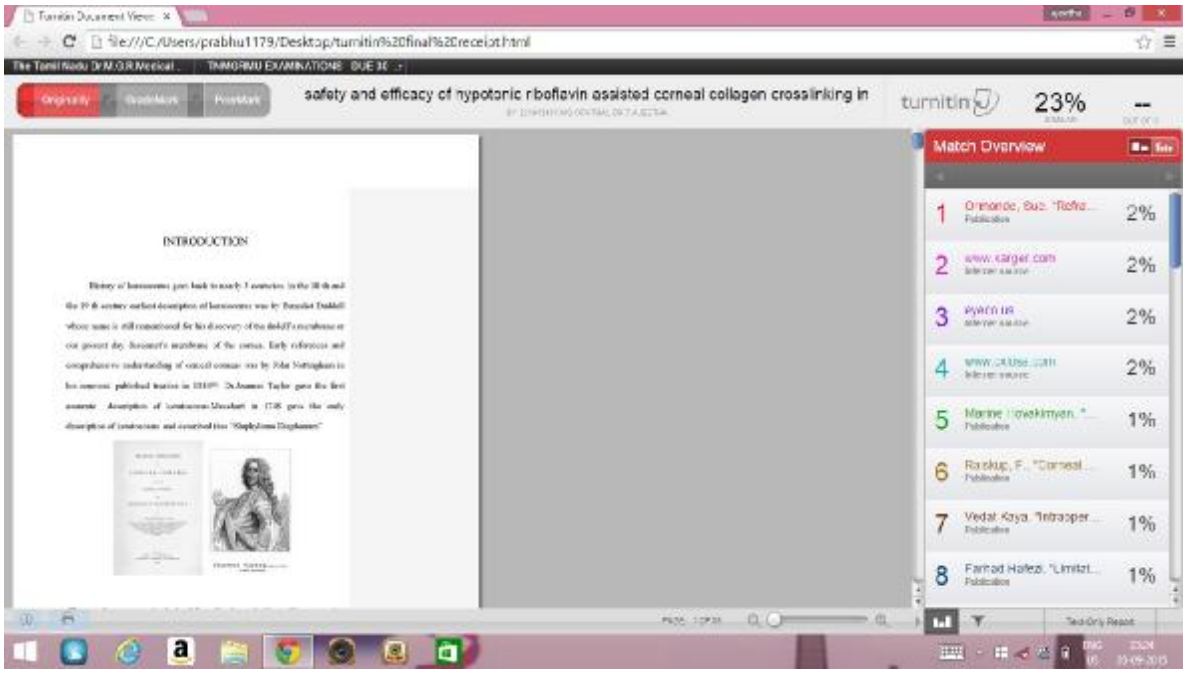
Surgeon :

Anaesthesia : Local Anaesthesia/General Aneasthesia

Technique : Hypotonic Riboflavin assisted C3R

ABBREVIATIONS

PKP	-	Penetrating Keratoplasty
DALK	-	Deep Anterior Lamellar Keratoplasty
INTACS	-	Intrastromal Corneal Segments
PRK	-	Photorefractive Keratectomy
CXL	-	Corneal Collagen Crosslinking
UCVA	-	Uncorrected Visual Acuity
BCVA	-	Best Corrected Visual Acuity
S E	-	Spherical Equivalent
K-Mean	-	Mean Keratometry
D	-	Diopter
UVA	-	Ultra Violet A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INTRODUCTION

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INTRODUCTION

S No.	MR No.	Pat Name	Age	Sex	Eye	Diagnosis	previous ocular history	UCVA	preoperative													procedure hypo C3R					immediate post op	
																	keratometry			specular microscopy				intraop pachymetry						
									sphere	cylinder	axis	BCVA	MSE	Vn with contacts	Tension	Fundus	K mean	astig	min thickness	cell count	Hexa	coeff var	SD	epi on	epi off	distilled water	rib instil	end of proc	stromal haze	days of epithelial healing
1	3127492	Thirumal	18	M	RE	K conus	cl lens ,LEc3r	5⁄60	-7.5	-6	30°	6⁄18	-10.5	66	7 mm	normal	56.0D	6.00D	396 µ	2907	39	49	170	400µ	379µ	403µ	382µ	376µ	present	3 days
2	3090172	revanth	24	M	LE	K conus	Cl lens ,REc3r	6⁄36		-3	90°	6⁄12	-1.5	66p	12mm	normal	55.2D	5.8D	372µ	2688	40	51	191	385µ	374µ	396µ	390µ	370µ	present	4 days
3	3854365	bagatsingh	19	M	LE	K conus	Cl wear	5⁄60	-1.5	-4	126°	6⁄24	-3.5	69	not done	normal	56.5D	4.4D	388µ	not done	not done	notdone	not done	not done	not done	notdone	notdone	notdone	present	3 days
4	3914081	sivanesan	10	M	LE	K conus	nil	3⁄60	-7	-3.5	180°	6⁄9	-8.75	6/12p	not done	normal	55.2D	3.5D	354µ	not done	not done	notdone	not done	374µ	360µ	410µ	404µ	364µ	present	4 days
5	3921283	Augustin	21	M	LE	K conus	glasses	6⁄36		-4.5	110°	6⁄18	-2.25	66	12mm	normal	62.4D	10.4D	380µ	not done	not done	notdone	not done	394µ	380µ	415µ	410µ	390µ	present	4 days
0	3932093	Saranya	25	F	LE	K conus	nil	6⁄36	-4	-1.5	180°	6⁄12	-4.75	6⁄9	12mm	normal	53.3D	2.4D	380µ	not done	not done	not done	not done	415µ	365µ	424µ	368µ	372µ	present	4 days
7	3852249	Anandkum	11	M	LE	K conus	vkc glass	4⁄60	-6	-3	90°	6⁄36	-7.5	cl intolerant	error	normal	58.5D	2.4D	350µ	2907	38	44	153	405µ	400µ	438µ	448µ	444µ	present	3 days
8	3820516	suganya	20	F	LE	K conus	nil	6⁄36		-3.5	90°	6⁄12	-1.75	66	not done	normal	51.2D	5.1D	385µ	2387	34	54	225	413µ	396µ	388µ	373µ	369µ	present	4 days
9	3945576	Albin varge	21	M	LE	K conus	nil	5⁄60	-5	-3	180°	6⁄18	-6.5	66	not done	normal	49.2D	2.8D	382µ	2907	40	39	135	392µ	388µ	396µ	379µ	365µ	present	4 days
10	3936344	Nagaraj	13	M	RE	K conus	nil	4⁄60	-8	-6	180°	6⁄18	-11	66	not done	normal	56.0D	8.1D	387µ	not done	not done	notdone	not done	379µ	361µ	381µ	387µ	426µ	present	3 days
11	2482638	Bharathi	17	F	RE	K conus	glasses	2⁄60	-9	-4	180°	66	-11	intolerant	10mm	normal	58.0D	5.1D	350µ	2915	50	38	129	not done	not done	notdone	notdone	notdone	present	3days
12	3918271	Melbin	13	M	LE	K conus	nil	2⁄60	-11	-6	120°	6⁄24	-14	6⁄12p	10mm	normal	56.4D	5.7D	390µ	not done	not done	notdone	not done	421µ	380µ	391µ	410µ	364µ	present	3days
13	3921618	Priya	21	F	RE	K conus	nil	2⁄60	-16.5	-4.5	15°	6⁄18	-18.75	6⁄9	12mm	normal	62.6D	9.1D	366µ	2793	53	40	143	402µ	364µ	410µ	384µ	373µ	present	3 days
14	3748120	Sameera	12	F	RE	K conus	vkc glass	5⁄60	-2.5	-4	70°	6⁄12p	-4.5	6⁄12	11mm	normal	61.8D	.1D	367µ	not done	not done	notdone	not done	401µ	388µ	420µ	409µ	470µ	present	3days
15	3972398	Aathika	15	F	LE	k conus	nil	5⁄60nip		-2.5	105°	6⁄18	-1.25	6/6p	not done	normal	68.3D	3.1D	369µ	not done	not done	notdone	not done	388µ	355µ	470µ	415µ	360µ	present	3days
16	3925543	akil reji	15	M	LE	K conus	nil	5⁄60	-3	-2	150°	6⁄18	-4	66p	10mm	normal	49.3D	2.5D	387µ	2913	51	36	130	not done	not done	notdone	notdone	notdone	present	3 days
17	2940414	rinto chack	19	F	LE	K conus	cl ,vkc	6⁄60	-4	-1.5	130°	6⁄9	-4.75	66	16mm	normal	53.2D	2.4D	391µ	not done	not done	notdone	not done	not done	not done	notdone	notdone	notdone	present	3days
18	3955952	aswathy	17	F	LE	kconus	nil	6⁄60		-2.5	105°	6⁄18	-1.25	6/6p	not done	normal	64.5D	5.7D	385µ	not done	not done	notdone	not done	404µ	404µ	424µ	444µ	366µ	present	3 days
19	3450864	dhivaya	18	F	RE	kconus	cl	6⁄36		-3	45°	6⁄6p	-1.5	66p	not done	normal	47.0D	5.7D	393µ	not done	not done	notdone	not done	not done	not done	notdone	notdone	notdone	present	3 days
20	3912251	samuvel	20	M	LE	kconus	nil	4⁄60		-5	170°	6⁄36	-2.5	66p	not done	normal	56.6D	7.8D	376µ	2786	69	43	248	405µ	379µ	408µ	428µ	415µ	stromal infiltrate	7 days
21	3848412	jayapriya	19	F	LE	kconus	vkc glass	6⁄60	-2	-4	180°	6⁄18	-6	66	10mm	normal	55.6D	5.4D	382µ	2500	50	38	150	422µ	394µ	403µ	410µ	377µ	present	3 days

							postoperative three months								
Sno	MR no.	Pat Name	sex	age	Eye	Diagnosis	UCVA	Sphere	cylinder	axis	BCVA	MSE	Vn with cl	Tension	slit lamp examination Corneal haze
1	3127492	Thirumal	18	M	RE	Keratoconus	4/60	-7.5	-3	30°	6/18	-9	6/6	error	stromal haze
2	3090172	revanth	24	M	LE	Keratoconus	6/36p		-3	90°	6/36	-1.5	6/6	10mm	stromal haze
3	3854365	bagatsingh	19	M	LE	Keratoconus	6/60	-1	-4	160°	6/24p	-3	not willing 12mm	12mm	stromal haze
4	3914081	sivanesan	10	M	LE	Keratoconus	6/60	-7	-3.5	180°	6/9	-8.75	not willin	12 mm	stromal scar
5	3921283	Augustin	21	M	LE	Keratoconus	6/60		-4.5	105°	6/12	-2.25	not comfortable		corneal thinning
6	3932093	Saranya	25	F	LE	Keratoconus	6/24	-4	-2	150°	6/9p	-5	6/6	14mm	min haze demarc lines
7	3852249	Anandkumar	11	M	LE	Keratoconus	3/60	-7	-3	90°	6/36	-8.5	not willing	error	absent
8	3820516	suganya	20	F	LE	Keratoconus	6/36	-1	-3.5	90°	6/12	-2.75	not willing11mm		min haze
9	3945576	Albin vargese	21	M	LE	Keratoconus	6/36	-2	-2.5	15°	6/18	-3.25	6/6	13mm	min haze demarc lines
10	3936344	Nagaraj	13	M	RE	Keratoconus	6/36	-6	-6	90°	6/12	-9	6/6	6mm	stromal haze pees
11	2482638	Bharathi	17	F	RE	Keratoconus	3/60	-11	-4	180°	6/6p	-13	6/6	10mm	antstrom scar
12	3918271	Melbin	13	M	LE	Keratoconus	3/60	-13.5	-3	120°	6/24	-14.5	not done	12mm	minimalhaze
13	3921618	Priya	21	F	RE	Keratoconus	6/60		-4	100°	6/18	-2	6/9	11mm	stromal haze
14	3748120	Sameera	12	F	RE	Keratoconus	6/60	-2.5	-4	60°	6/18	-4.5	6/12	11mm	minimal haze
15	3972398	Aathika	15	F	LE	Keratoconus	4/60		-3	105°	6/18	-1.5	6/6p	12mm	minimal haze
16	3925543	akil reji	15	M	LE	Keratoconus	6/36	-1	-2.5	150°	6/12p	-2.75	6/6p	10mm	min haze
17	2940414	rintochacko	19	F	LE	Keratoconus	6/24	-4.5	-1.5	130°	6/9	-5.25	6/6	error	min haze
18	3955952	aswathy	17	F	LE	Keratoconus	5/60		-3	105°	6/18	-1.5	6/6p	11mm	min haze
19	3450864	dhivaya	18	F	RE	Keratoconus	6/36		-3	45°	6/6p	-1.5	6/6	not done	min haze
20	3912251	samuvel	20	M	LE	Keratoconus	5/60		-5.5	110°	6/18	-2.75	6/6p	8mm	stromalscar demarcation lines
21	3848412	jayapriya	19	F	LE	Keratoconus	5/60	-3	-3	180°	6/9	-4.5	6/6	10mm	min haze

Sno	MR no.	Pat Name	sex	age	Eye	Diagnosis	postoperative six month															
															keratometry				Specular Microscopy			slit lamp exam
							UCVA	Sphere	cylinder	axis	BCVA	MSE	Vn with cl	Tension	k mean	astigmatism	minimal thickness	cell count	hexa	coeff of var	SD	stromal haze
1	3127492	Thirumal	18	M	RE	keratoconus	4⁄60	-7	-4	30°	6⁄12	-9	6⁄6	14mm	55.5D	7.00D	251µ	2653	40	40	174	stromal hze
2	3090172	Saikumar	24	M	LE	keratoconus	6⁄60		-3	90°	6⁄36	-1.5	6⁄6p	10mm	52.5D	5.5D	315µ	2688	40	51	191	stromal haze
3	3854365	bagatsingh	19	M	LE	keratoconus	6⁄12		-1.5	165°	6⁄6	-0.75	6⁄6	not done	52.4D	4.0D	293µ	not done				min haze
4	3914081	sivanesan	10	M	LE	keratoconus	4⁄60	-7	-3.5	180°	6⁄9	-8.75	not willing	10mm	55.7D	2.7D	174µ	error				stromal scar
5	3921283	Augustin	21	M	LE	keratoconus	6⁄60		-4	105°	6⁄12p	-2	notwilling	12mm	60.1D	9.3D	250µ	not done				stromal haze
6	3932093	Saranya	25	F	LE	keratoconus	6⁄36	-4	-1.5	180°	6⁄6	-4.75	6⁄6	12mm	52.9D	1.6D	333µ	2560	43	50	193	nebular opacity
7	3852249	Anandkumar	11	M	LE	keratoconus	4⁄60	-7	-3	90°	6⁄36	-8.5	intolerant	12mm	59.7D	4.8D	298µ	2874	31	73	253	nebular opacity
8	3820516	suganya	20	F	LE	keratoconus	6⁄60	-1	-3.5	70°	6⁄9	-2.75	not willing	not done	48.5D	6.2D	345µ	2667	33	63	243	stromal haze
9	3945576	Albin vargese	21	M	LE	keratoconus	6⁄36	-2	-2.5	15°	6⁄6	3.25	6⁄6	not done	50.7D	2.8D	346µ	2907	40	39	135	stromal haze
10	3936344	Nagaraj	13	M	RE	keratoconus	6⁄36	-6	-6	90°	6⁄12	-9	6⁄6	6mm	55.9D	5.4d	299µ	3058	52	37	120	stromal haze
11	2482638	Bharathi	17	F	RE	keratoconus	3⁄60	-11	-4	180°	6⁄6p	-13	6⁄6	10mm	58.9D	3.7D	242µ	2800	33	49	143	faint scar
12	3918271	Melbin	13	M	LE	keratoconus	2⁄60	-13	-3	120°	6⁄18	-14.5	6⁄12	11mm	53.2D	5.3D	355µ	2597	32	46	176	stromal haze
13	3921618	Priya	21	F	RE	keratoconus	5⁄60	-3	-6	170°	6⁄36	-6	6⁄12	10mm	62.1D	10.4D	347µ	2119	38	46	217	stromal haze
14	3748120	Sameera	12	F	RE	keratoconus	5⁄60	-2.5	-4	50°	6⁄18	-4.5	6⁄9	error	62.8D	2.2D	345µ	3717	32	46	176	stromal haze
15	3972398	Aathika	15	F	LE	keratoconus	6⁄60		-2.5	105°	6⁄6p	-1.25	6⁄6	10mm	65.7D	3.5D	342µ	not done				apical scar
16	3925543	akil reji	15	M	LE	keratoconus	6⁄36	-0.5	-3	150°	6⁄6p	-2	6⁄6p	10mm	47.2D	3.0D	255µ	2653	22	47	179	stromal haze
17	2940414	rintochacko	19	F	LE	keratoconus	6⁄60	-4.5	-1.5	130°	6⁄9	-5.25	6⁄6	14mm	49.5D	2.3D	341µ	not done				min haze
18	3955952	aswathy	17	F	LE	keratoconus	6⁄60		-3	135°	6⁄24	-1.5	6⁄9	10mm	63.8D	4.00D	342µ	2851	41	43	153	apical scarring
19	3450864	dhivaya	18	F	RE	keratoconus	6⁄36		-3	45°	6⁄6p	-1.5	6⁄6	11mm	45.4D	5.4D	351µ	not done				min haze
20	3912251	samuvel	20	M	LE	keratoconus	5⁄60		-5.5	110°	6⁄6p	-2.75	6⁄6	10mm	49.1D	8.6D	332µ	2500	34	52	208	stromal haze nebular opacity
21	3848412	jayapriya	19	F	LE	keratoconus	5⁄60	-3	-3	180°	6⁄9p	-4.5	6⁄6p	10mm	49.7D	6.1D	330µ	2203	44	52	234	stromal haze